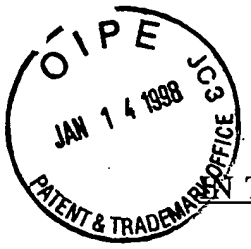


IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re U.S. Patent of:

Scott M. Rocklage, et al.

U.S. Serial No.: 07/047,614
Filed: May 8, 1987

U.S. Patent No.: 4,933,456
Issued: June 12, 1990

For: DIPYRIDOXYL PHOSPHATE NMRI CONTRAST AGENTS

Group Art Unit: 121

Examiner: Alan L. Rothman

SUBMISSION OF APPLICATION FOR EXTENSION OF PATENT TERM UNDER 35 U.S.C. § 156

Hon. Commissioner of Patents and Trademarks
Washington, D.C. 20231

Sir:

Nycomed Salutar, Inc., a corporation organized and existing under the laws of the State of California, having its principal office and place of business at 466 Devon Park Drive, Wayne, PA 19087-8630 (hereinafter "Applicant"), by change of name from Salutar, Inc., the assignee of record in the above-identified patent as recorded on May 8, 1987 at Reel 4750, Frame 972 in the Assignment Records of the U.S. Patent and Trademark Office and the owner of all right, title and interest in and to the above-identified patent, submits herewith the following papers in

CERTIFICATE OF MAILING UNDER 37 CFR 1.10

I hereby certify that this document (along with any referred to as being attached or enclosed) is being deposited with the United States Postal Service on the date shown below with sufficient postage as Express Mail (Label No. EM424912382US) in an envelope addressed to the Hon. Commissioner of Patents and Trademarks, Washington, D.C., 20231.

Date: Jan 14, 1998 Sent by: Cynthia B. Pacheco Signature: Cynthia B Pacheco

support of an Application For Extension of Patent Term Under 35 U.S.C. § 156 with respect to the above-identified patent:

(1) Power of Attorney from Nycomed Salutar, Inc. to inter alia, the undersigned attorney (it should be noted that the Power of Attorney submitted with original copy #1 of these papers is the original, executed Power of Attorney).

(2) Application for Extension of Patent Term Under 35 U.S.C. § 156 including:

Exhibit 1 - Package insert describing the approved product;
Exhibit 2 - Copy of the above-identified patent;
Exhibit 3 - Copy of Certificate of Correction;
Exhibit 4 - Evidence of Payment of Maintenance Fees
Exhibit 5 - Brief description of significant activities during the applicable regulatory review period.

(3) Declaration of John Kappos.

(4) Certificate that these application papers are being submitted in duplicate.

(5) Check (no. 4281) in the amount of $1,120.00 to the Commissioner of Patents and Trademarks to cover the prescribed fee.

Please charge Deposit Account No. 12-2475 for any fee deficiency and credit same for any overpayment.

Respectfully submitted,

LYON & LYON LLP

Date: January 14, 1998

By John Kappos
John Kappos
Reg. No. 37,861
Attorneys for Applicants

JCK/cp
633 West Fifth Street, 47th Floor
Los Angeles, CA 90071-2066
(714) 751-6606 or (213) 489-1600

#21

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re U.S. Patent of:

Scott M. Rocklage, et al.

U.S. Serial No.: 07/047,614
Filed: May 8, 1987

U.S. Patent No.: 4,933,456
Issued: June 12, 1990

For: DIPYRIDOXYL PHOSPHATE NMRI CONTRAST AGENTS

Group Art Unit: 121

Examiner: Alan L. Rothman

APPLICATION FOR EXTENSION OF PATENT TERM UNDER 35 U.S.C. § 156

Hon. Commissioner of Patents and Trademarks
Washington, D.C. 20231

Sir:

Nycomed Salutar, Inc., a corporation organized and existing under the laws of the State of California, having its principal office and place of business at 466 Devon Park Drive, Wayne, PA 19087-8630 (hereinafter "Applicant"), by change of name from Salutar, Inc., the assignee of record in the above-identified patent (hereinafter "The Patent") as recorded on May 8, 1987 at Reel 4750, Frame 972, in the Assignment Records of the U.S. Patent trademark Office, and the owner of all right, title and interest in and to The Patent, hereby applies, through undersigned counsel, for extension of the term of The Patent under 35 U.S.C. § 156 on the basis

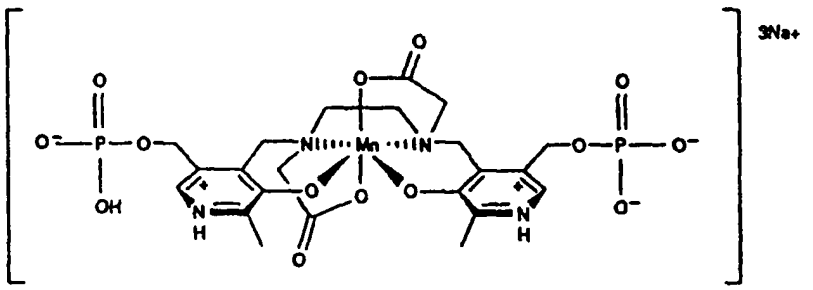
CERTIFICATE OF MAILING UNDER 37 CFR 1.10

I hereby certify that this document (along with any referred to as being attached or enclosed) is being deposited with the United States Postal Service on the date shown below with sufficient postage as Express Mail (Label No. EM424912382US) in an envelope addressed to the Hon. Commissioner of Patents and Trademarks, Washington, D.C., 20231.

Date: Jan 14, 1998 Sent by: Cynthia B. Pacheco Signature: Cynthia B Pacheco

of the following information submitted in accordance with the provisions of 37 CFR § 1.740(a)(1)-(17) set forth in the sequence of those subparagraphs. Filed herewith is a Power of Attorney authorizing the undersigned to file and prosecute this Application for Extension of Patent Term under 35 U.S.C. § 156, and to transact all business in relation thereto.

(1) This application for extension is based upon the regulatory review period before the FDA of Applicant's approved product, "Teslascan" (mangafodipir trisodium) injection, suitable for use as a contrast agent for hepatic magnetic resonance imaging (MRI) in adults for intravenous administration. Mangafodipir trisodium (the official USAN name) is trisodium trihydrogen (*OC*-6-13)-[[*N*,*N*'-1,2-ethanediylbis(N-[[3-hydroxy-2-methyl-5-[(phosphonooxy)methyl]-4-pyridinyl]methyl]glycinato]] (8-)] manganate (6-) with a molecular weight of 757.33 (anhydrous), an empirical formula of $C_{22}H_{27}MnN_4Na_3O_{14}P_2$ (anhydrous) and the structure:



"Teslascan" (mangafodipir trisodium) injection's use as an MRI contrast enhancing agent is more particularly described in the package insert attached hereto as EXHIBIT 1.

(2) The approved product "TESLASCAN" (mangafodipir trisodium) was subject to regulatory review under the Federal Food, Drug and Cosmetic Act, Section 505 (21 U.S.C. § 355).

(3) The approved product "TESLASCAN" (mangafodipir trisodium) injection received permission for commercial marketing or use after a regulatory review period under Section 505 of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355) on November 26, 1997.

(4) The active ingredient in the approved product "TESLASCAN" (mangafodipir trisodium) injection is mangafodipir trisodium. To the best of Applicant's knowledge, the permission for the commercial marketing or use of this product after such regulatory review period is the first permitted commercial marketing or use of such product under the Federal Food, Drug and Cosmetic Act.

(5) This application for extension of patent term under 35 U.S.C. § 156 is being submitted within the permitted 60 day period, which period will expire on January 24, 1998.

(6) The patent for which an extension is being sought ("The Patent")[1/] is as follows:

U.S. Patent No. 4,933,456
Issued: June 12, 1990
Expires: June 12, 2007
Inventors: Scott M. Rocklage and Steven C. Quay

(7) A copy of The Patent, including the entire specification, claims and drawings, is attached hereto as EXHIBIT 2.

(8) There is no terminal disclaimer or reexamination certificate in The Patent. A copy of a certificate of correction, dated October 23, 1993, is attached hereto as EXHIBIT 3. All maintenance fee payments due have been made for this patent. A copy of The Patent maintenance fee file from the Patent Application Locating and Monitoring (P.A.L.M.) System at the Patent and Trademark Office ("PTO") evidencing the payments made on December 22, 1993 and December 8, 1997 is attached hereto as EXHIBIT 4, together with a letter from the PTO, dated January 9, 1998, evidencing that the maintenance fees in The Patent are paid current.

[1/] Although not required by 37 C.F.R. §1.740(a), we note that further patents have issued from applications related to The Patent, none of which has been extended based on the regulatory review period that is the subject of this extension application. These patents, all of which are divisional applications, with the exception of the first listed which is a continuation-in-part, are as follows: U.S. Pat. Nos. (i) 4,863,716, (ii) 4,992,555, (iii) 4,992,554, (iv) 5,091,169, (v) 5,130,431 and (vi) 5,223,243.

(9) The Patent claims, "[a] metal ion chelate of a chelating compound . . . or . . . a physiological or biocompatible inorganic or organic salt [thereof] . . ." comprising, inter alia, "TESLASCAN" (mangafodipir trisodium) (Claims 1-6 and 9-12[2/]).

[2/] It is to be noted that there were three inadvertent errors in designating the structure of the compound of claim 1 that arose during prosecution. One error, the inadvertent replacement of the OH group appended to the left-handed pyridine ring, in the position meta to the pyridynl nitrogen, with a CH group was corrected in the Certificate of Correction attached hereto as EXHIBIT 3. Applicant will submit another Certificate of Correction to correct the other two recently discovered errors, the inadvertent elimination of the subscript "2" from the hydrogen in the formulas for R and R_1 in claim 1. The correct representations of R and R_1 appear in the specification at Column 3, lines 37-48.

(10) The relevant dates and information pursuant to 35 U.S.C. §156(g) in order to enable the Secretary of Health and Human Services to determine the applicable regulatory review period are as follows:

(i) Issue date of Patent: June 12, 1990

(ii) Effective Date of IND application:
Submitted April 4, 1989
Received April 10, 1989
Effective May 10, 1989
(IND #33,031 assigned by FDA)

(iii) NDA #20-652
Submitted September 8, 1995
(effective November 7, 1995).

(iv) NDA #20-652 approved November 26, 1997

(11) A brief description of the significant activities undertaken by or on behalf of the Applicant during the applicable regulatory review period with respect to the approved product, and the significant dates applicable to such activities, are set out in EXHIBITS 5A & 5B.

(12) Applicant is of the opinion that The Patent is eligible for extension under 35 U.S.C. § 156 because it satisfies all the requirements for such extension, inasmuch as:

(i) Such patent claims a human drug product [35 U.S.C. §156(a)];

(ii) The term of such patent has not expired before the submission of this application [35 U.S.C. § 156(a)(1)];

(iii) The term of such patent has never been extended [35 U.S.C. § 156(a)(2)],

(iv) The application for extension is submitted by the owner of record of The Patent, through undersigned counsel, in accordance with the requirements of 35 U.S.C. § 156(d);

(v) The approved product, "TESLASCAN" (mangafodipir trisodium) injection, has been subject to a regulatory review period before its commercial marketing or use [35 U.S.C. § 156(a)(4)];

(vi) The permission for the commercial marketing or use of the product, "TESLASCAN" (mangafodipir trisodium) injection, after the regulatory review period, is the first permitted commercial marketing or use of the approved product under the provisions of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. § 355) under which such regulatory review period occurred; and

(vii) No other patent has been extended for the same regulatory review period for the product "TESLASCAN" (mangafodipir trisodium) injection [35 U.S.C. § 156(c)((4)].

Applicant requests an extension of the patent term of The Patent by 4 years (1461 days) and approximately 5½ months (167 days) from the original expiration date of June 12, 2007 to November 26, 2011. This period of extension is calculated according to the following subsections of 37 CFR § 1.775:

(a) The original expiration date of The Patent is 17 years from its date of issue, that is June 12, 2007.

(b) The term for a patent for a human drug will be extended by the length of the regulatory review period, as calculated in subsection (c) below, reduced as appropriate pursuant to subsection (d) below.

(c) The length of the regulatory review period was 3123 days, calculated as follows:

(1) The number of days from the effective date of original IND # 33,031 for "TESLASCAN" (mangafodipir trisodium) injection to the submission of NDA 20-652, that is from May 10, 1989 to September 8, 1995, is 2313 days.

(2) The number of days between initial submission of the NDA to the approval of the NDA, that is from September 8, 1995 to November 26, 1997 is 810 days.

(d) The term of The Patent as extended for a human drug product is to April 13, 2012, that is an extension of 1767 days, calculated by subtracting 1356 days as follows from the 3123 days of the total regulatory review period from subparagraph (c):

(1) From the number of days of the regulatory review period calculated under subparagraph (c), the following are subtracted:

i) 399 days of the regulatory review period that was on or before the date on which the patent issued;

ii) Applicant believes it acted with diligence in this matter as evidenced by EXHIBITS 5A & 5B;

iii) One half the period defined by paragraph (c)(1) after that period is reduced by the period defined in paragraph (d)(1)(i), ignoring half days, comes to 957 days.

(2) Adding 1767 days to the original expiration date of June 12, 2007 comes to April 13, 2012.

(3) Adding 14 years to the date of approval of the NDA comes to November 26, 2011.

(4) The earlier of the dates calculated under subparagraphs (d)(2) and (3) above is November 26, 2011.

(5) The Patent was issued after September 24, 1984.

i) Adding 5 years to the original expiration date of The Patent comes to June 12, 2012.

ii) Comparing the dates obtained pursuant to paragraphs (d)(4) and (d)(5)(I) above, the earlier of these dates is November 26, 2011.

(13) Applicant, through its undersigned counsel, acknowledges a duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services any information which is material to the determination of entitlement to the extension sought, in accordance with 37 CFR § 1.765.

(14) A check in the amount of $1,120.00 payable to the Commissioner of Patents and Trademarks is attached to cover the fee prescribed by 37 CFR § 1.20(j)(1) for receiving and acting upon this application for extension. The Commissioner is hereby authorized to charge any deficiency, or credit any surplus, in the amount indicated above relative to the required fee to our Deposit Account No. 12-2475.

(15) Please direct all inquiries and correspondence relating to this application for patent term extension to:

John Kappos
Lyon & Lyon LLP
633 West Fifth Street, 47th Floor
Los Angeles, CA 90071-2066
(714) 751-6606 or (213) 489-1600.

(16) Submitted herewith is a certification that these application papers are being submitted in duplicate.

(17) Additionally submitted herewith is a declaration of John Kappos, patent counsel for Applicant, pursuant to 37 CFR § 1.740(b)(1), authorized by the Power of Attorney executed by Applicant submitted herewith.

Respectfully submitted,

LYON & LYON LLP

Date: January 14, 1998

By _____
John Kappos
Reg. No. 37,861
Attorneys for Applicants

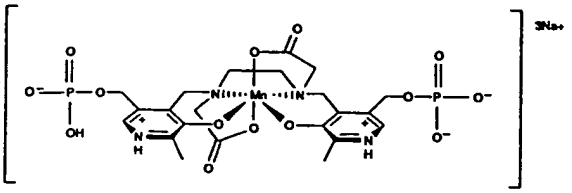
JCK/cp
633 West Fifth Street, 47th Floor
Los Angeles, CA 90071-2066
(714) 751-6606 or (213) 489-1600

TESLASCAN® 50 μmol/mL
(mangafodipir trisodium) Injection

DESCRIPTION

TESLASCAN® (mangafodipir trisodium) Injection is an intravenous contrast agent for magnetic resonance imaging.

TESLASCAN Injection is formulated with mangafodipir trisodium, a solution of trisodium trihydrogen (*OC*-6-13)-[[*N*,*N*'-1,2-ethanediylbis[*N*-[[3-hydroxy-2-methyl-5-[(phosphonooxy)methyl]-4-pyridinyl]methyl]glycinato]] (8-)] manganate (6-). Mangafodipir trisodium ($C_{22}H_{23}MnN_4Na_3O_{14}P_2$) has a molecular weight of 757.33 (anhydrous) and the manganese content of the molecule is 7.25%. Its structural formula is illustrated below:



TESLASCAN Injection is a sterile, clear yellow solution. Each milliliter of TESLASCAN Injection contains 37.9 mg (or 50 μmol/mL) mangafodipir trisodium; ascorbic acid, 2.0 mg; sodium chloride, 2.0 mg; fodipir, 0.25 mg; and Water for Injection. The pH is adjusted to 8.8 ± 0.4 with hydrochloric acid and/or sodium hydroxide. The osmolality is 298 mOsmol/kg water. TESLASCAN Injection does not contain a preservative.

Pertinent physicochemical data are provided below:

PHYSICOCHEMICAL DATA

	@ 37°C
Viscosity (cP)	0.8
Density (g/mL)	1.02
Specific Gravity	1.03
Osmolality (mOsmol/kg water)	298

CLINICAL PHARMACOLOGY

GENERAL

TESLASCAN Injection (mangafodipir trisodium) is a complex formed between a chelating agent (fodipir) and a paramagnetic metal ion, manganese. Mangafodipir shortens the spin lattice (longitudinal) relaxation time (T_1) of targeted tissues during MRI, leading to an increase in signal intensity (brightness) of the tissues.

PHARMACOKINETICS

Mangafodipir has two components: fodipir and a manganese (II) ion. Each has different pharmacokinetics, metabolism, and modes of elimination. After intravenous administration of TESLASCAN, the pharmacokinetics of each component were investigated.

Fodipir: When TESLASCAN is labeled with the ^{14}C-label residing in the fodipir, after a single intravenous dose of 5 μmol/kg of ^{14}C-TESLASCAN in 6 healthy volunteer men, the mean ± SD area under the radioactivity plasma concentration curve (AUC) is 22.7 ± 3.2 μg*h/mL.

Manganese (II) ion: Generally, the total body store of manganese in adults is 20 mg. Most of this is from dietary intake (2-5 mg/day). TESLASCAN Injection contains 2.75 mg/mL of chelated manganese. In a 70 kg adult, 5 μmol/kg of TESLASCAN Injection contains 19.2 mg of chelated manganese. Therefore, a single injection of TESLASCAN will approximately double the total body store of manganese before excretion occurs. In a study of 31 healthy volunteers (16 men and 15 women), after a single intravenous dose of 5 μmol/kg TESLASCAN, areas under the manganese serum concentration versus time curves (AUC) were 15.8 ± 5.8 μM*h (mean ± SD) and 16.0 ± 2.9 μM*h (mean ± SD), respectively. (See Elimination section for details on excretion.)

DISTRIBUTION

Mangafodipir itself does not bind to plasma proteins *in vitro*; however, manganese (II) and manganese (III) are known to bind to plasma proteins *in vitro*.

In pregnant rats who received ^{54}Mn, radioactivity was detected in the placenta and in the fetus. (See Pregnancy section.)

METABOLISM

After intravenous injection, mangafodipir trisodium is metabolized by the removal of two phosphate groups and the exchange of the manganese ion for an endogenous zinc ion. This produces two major metabolites, manganese dipyridoxyl ethylenediamine diacetic acid (MnPLED) and zinc dipyridoxyl ethylenediamine diacetic acid (ZnPLED).

In plasma, the mangafodipir trisodium is not detected after 2 hours. The MnPLED concentration peaks within ten minutes and is not detected after 1 hour. The ZnPLED metabolite reaches maximum concentration 20 minutes after injection and then decreases slowly. By 24 hours the two major metabolites (MnPLED and ZnPLED) represent 12% and 57% of the administered dose, respectively.

ELIMINATION

Fodipir: When TESLASCAN is labeled with the ^{14}C in the fodipir, after intravenous administration of 5 μmol/kg ^{14}C-mangafodipir trisodium to 6 healthy volunteer men, approximately 92% of the radioactivity administered is eliminated in the urine over 24 hours. Negligible amounts (0.3%) are recovered in feces over 168 hours. The total plasma clearance of radioactivity was 11.6 ± 2.1 L/h (0.15 ± 0.02 L/h/kg mean ± SD). The apparent terminal half-life (mean ± SD) of elimination of radioactivity from plasma is 2.09 ± 0.47 hours.

Manganese (II) ion: After intravenous administration of TESLASCAN, the initially high serum manganese concentrations drop rapidly and approach detection limits (or baseline levels) within a few hours. Approximately 15% of the dose administered of the manganese (II) ion of mangafodipir is eliminated in the urine within the first 24 hours after injection and an additional 59% is excreted in the feces over the following 5 days. The remainder is eliminated in urine and feces gradually.

The dialyzability of TESLASCAN Injection and its metabolites has not been studied.

SPECIAL POPULATIONS

Hepatic Insufficiency: A single intravenous dose of 5 μmol/kg of TESLASCAN was administered to 31 subjects with normal hepatic function (16 men and 15 women) and 10 subjects with impaired hepatic function (5 men and 5 women). In the patients with impaired hepatic function (5 men and 5 women), after a single intravenous dose of 5 μmol/kg TESLASCAN, for manganese, AUCs were 23.3 ± 4.3 μM*h (mean ± SD) and 24.6 ± 4.0 μM*h (mean ± SD), respectively. (See Pharmacokinetics of Manganese Ion for comparative values in healthy volunteers.)

Manganese (II) ion serum levels at 1 hour after injection were 10% or less of maximal values.

Manganese (II) ion half-life: In both healthy subjects and subjects with hepatic impairment, the immediate distribution half-life (determined over the interval from 5 minutes to 2 hours after injection) was 24.4 ± 7.7 min (mean ± SD). However, the terminal half-lives were longer, $t_{1/2}$ = 10.1 ± 20.3 hrs and $t_{1/2}$ = 26.7 ± 19.0 hrs, respectively, for healthy and hepatically impaired subjects.

GENDER

Statistically significant differences were not detected in the elimination half-lives between men and women who were either healthy or had hepatic impairments, nor were there differences in the overall urinary or fecal recovery of manganese (II) ion in men and women who were either healthy or had hepatic impairments. (See Table 1 for details.)

TABLE 1: SIMILARITY IN ELIMINATION PROFILES OF NORMAL AND HEPATICALLY IMPAIRED MEN AND WOMEN (mean ± SD)

Population	Elimination $t_{1/2}$		Urine or Fecal Recovery*	
	Men	Women	Men	Women
Healthy Volunteers	13.9 ± 27.4	5.8 ± 4.0	73.9 ± 22.8	73.4 ± 22.9
Hepatically Impaired	30.6 ± 16.6	22.9 ± 22.3	77.8 ± 14.7	66.6 ± 9.8

* Collected over 0 - 5 days

AGE

Pharmacokinetic differences due to age in adults or in pediatric patients after intravenous TESLASCAN were not studied.

RACE

Pharmacokinetic differences due to race after intravenous TESLASCAN were not studied.

DRUG-DRUG INTERACTIONS

Drug interactions were not studied.

DIETARY EFFECTS

Pharmacokinetic studies with intravenous TESLASCAN were performed with nonfasted volunteers or patients.

PHARMACODYNAMICS

Mangafodipir enhances T_1 signal intensity. In a study of 12 healthy volunteer men, mangafodipir began to increase the signal intensity of liver tissue within 1-3 minutes, and steady-state enhancement was reached in about 5-10 minutes. Liver enhancement after TESLASCAN Injection administration is detectable in patients up to 24 hours after injection. After mangafodipir trisodium administration, liver lesions may present in a number of different patterns of contrast enhancement. (See Clinical Trials section.)

CLINICAL TRIALS

TESLASCAN Injection was studied in four multicenter, randomized, blinded, controlled clinical trials in a total of 546 adults who underwent hepatic MRI for evaluation of known or suspected focal liver disease.

EXHIBIT 1

In two of these studies, 404 adults (244 men, 160 women; 79% Caucasian, 10% Black, 6% Asian, 5% other races; mean age 58; range, 19-86 yr) received TESLASCAN 5 μmol/kg. Of these, 369 patients had images that were evaluated for efficacy.

All patients were imaged in three ways: 1) by contrast-enhanced computed tomography (CECT), 2) by unenhanced magnetic resonance imaging (MRI) and 3) by TESLASCAN Injection MRI. TESLASCAN Injection MRIs were obtained 15 minutes after injection (median, 20 minutes; range, 2-134 minutes). The sets of images were evaluated blindly as CECT alone, unenhanced MR images alone, TESLASCAN-enhanced MR images alone, and paired comparisons of the unenhanced and TESLASCAN-enhanced MRIs. Each liver lesion identified was rated for the presence of a specific cellular process (hepatocellular, nonhepatocellular, malignant, nonmalignant, or uncertain disease); a specific diagnosis (focal nodular hyperplasia, regenerative nodule, fatty infiltration, hepatoma/hepatocellular carcinoma, metastasis, cyst, adenoma, hemangioma or unknown); and the lesion's pattern of enhancement (homogeneous, inhomogeneous, central, peripheral thin rim, peripheral thick rim, peripheral linear foci, peripheral nodular, or no enhancement). Histopathology was obtained for some lesions. An overall final diagnosis was based on clinical, histopathologic, and all imaging information except the TESLASCAN MRI. The analysis is based on the extent of agreement between the diagnosis from the TESLASCAN MRI versus the histopathologic diagnosis for each lesion, the correct number of lesions detected, and the diagnosis of each lesion or disease state. The results are reported as complete agreement (with all lesions and diagnoses) or essential agreement (with diagnoses but not necessarily all lesions).

Based upon these two studies, TESLASCAN Injection enhanced MRI contrast on the T_1-weighted pulse sequences. Table 2 shows the proportions of patients for whom the imaging diagnosis had complete or essential agreement with the final diagnosis. In both studies TESLASCAN MRI alone and the paired reading of TESLASCAN MRI each had a statistically significant higher extent of agreement with the final diagnosis than did unenhanced MRI.

TABLE 2: OVERALL PERCENT OF TOTAL OR ESSENTIAL AGREEMENT OF IMAGE RESULTS[1] WITH THE FINAL CLINICAL DIAGNOSIS[2] IN 2 STUDIES

STUDY		TESLASCAN MRI vs. UNENHANCED MRI	PAIRED TESLASCAN MRI vs. UNENHANCED MRI
Study A	N Patients	187[3]	187
	% Agreement	71 vs. 63	74 vs. 63
	P value	(*P*<.020)	(*P*<.001)
Study B	N Patients	182[4]	182
	% Agreement	57 vs. 50	59 vs. 50
	P value	*P* = 0.04	(*P*<0.01)

[1] Obtained with CECT, unenhanced MRI, TESLASCAN MRI, and the paired read of unenhanced and TESLASCAN images.

[2] Using all available clinical information except the TESLASCAN MRI. Histopathology was the basis of the final diagnosis in 105 (25%) of the patients.

[3] 15 (7%) of the 202 patients in study A were not evaluable (7 withdrew, 8 did not have full data sets).

[4] 20 (10%) of the 202 patients in study B were not evaluable (12 withdrew, 8 did not have full data sets).

TABLE 3: COMPARISON OF PROPORTION OF CORRECTLY CHARACTERIZED LESIONS WITH HISTOPATHOLOGIC CONFIRMATION N = 105 LESIONS

	Detected by Imaging		Not Detected by Imaging
	Correctly Characterized	Not Correctly Characterized	
Paired TESLASCAN MRI*	51 (49%)	32 (27%)	22 (32%)
Unenhanced MRI	28 (30%)	48 (46%)	29 (33%)
CECT	28 (21%)	34 (28%)	35 (34%)

* Of the 105 histopathologically confirmed lesions, 83 (78%) detected lesions were detected by paired TESLASCAN MRI. Of these 83, 51 (62%) were correctly characterized by the paired TESLASCAN MRI and 28 (39%) by the unenhanced MRI or CECT (statistically significant).

In the above two studies, 105 individual lesions had histopathologic confirmation. Of these confirmed lesions, the proportion of correctly detected and correctly characterized lesions is shown in Table 3.

In two other studies of patients who received 5 μmol/kg of TESLASCAN, the efficacy of TESLASCAN Injection during delayed imaging was evaluated. In these two studies, 142 adult patients were given TESLASCAN (84 men, 58 women; 77% Caucasian, 15% Black, 4% Asian, 4% other races; mean age 58; range, 24-83 years). TESLASCAN-enhanced images for 140 patients were blindly evaluated for efficacy. TESLASCAN MRI imaging was performed at 15 minutes, 4 hours, and 24 hours after injection. The contrast enhancement results were comparable to those in the above studies and were similar at all time points.

In all four studies, each individual lesion's pattern of enhancement was coded as homogeneous, inhomogeneous, central, peripheral thin rim, peripheral thick rim, peripheral linear foci, peripheral nodular, or no enhancement. For the majority of histopathologically confirmed lesions, the pattern of TESLASCAN enhancement correlated with the hepatocellular disorders (having homogeneous, inhomogeneous, or central enhancement) or with the nonhepatocellular disorders (having peripheral or no enhancement). In the 121 patients who had malignant disease, 58 (47.9%) did not enhance, 20 (16.5%) were inhomogeneous, 15 (12.4%) had a thin peripheral rim, 12 (9.9%) had a thick peripheral rim, 12 (9.9%) were homogeneous and 4 (3.3%) had a variety of other patterns. For the 24 patients with nonmalignant disease, 13 (54%) did not enhance, 8 (33.3%) had homogenous patterns, and 3 (12%) had a variety of other patterns. Table 4 shows the patterns of enhancement that are seen in patients with histologically confirmed hepatocellular or nonhepatocellular disease.

Malignancy cannot be distinguished by the pattern of enhancement, or by the presence or absence of enhancement.

TABLE 4: PATTERN OF TESLASCAN CONTRAST ENHANCEMENT SEEN IN 147 PATIENTS WITH HISTOPATHOLOGICALLY CONFIRMED HEPATOCELLULAR & NONHEPATOCELLULAR LESIONS [1,2] FOR 4 STUDIES[3].

Pattern	Hepatocellular disorders N = 68 patients	Nonhepatocellular disorders N = 79 patients
Homogeneous	17 (25%)	3 (4%)
Inhomogeneous	22 (32%)	1 (1%)
No enhancement	16 (24%)	56 (71%)
Other Patterns[4]	13 (19%)	19 (24%)

[1] Reproducible patterns useful in distinguishing malignant and benign disease were not detected.

[2] Reproducible patterns useful in distinguishing specific hepatocellular and non-hepatocellular diseases were not detected.

[3] Overall, 147/546 (27%) of the patients had completely evaluable data sets and histopathology.

[4] Peripheral pattern subtypes of thick, thin, linear or nodular were inconsistent; central patterns were reported in 2 patients only.

INDICATIONS AND USAGE

TESLASCAN Injection is indicated for intravenous administration as an adjunct to MRI in patients to enhance the T_1-weighted images used in the detection, localization, characterization, and evaluation of lesions of the liver.

CONTRAINDICATIONS

TESLASCAN Injection is contraindicated in patients with known allergic or hypersensitivity reactions to manganese, fodipir or any of the inert ingredients.

WARNINGS

Patients with a history of drug reactions to contrast media, other allergies, or immune system disorders should be observed for several hours after drug administration.

A fully equipped emergency cart, or equivalent supplies and equipment, and personnel competent in recognizing and treating anaphylactic reactions should be available.

Caution should be exercised before administering TESLASCAN to patients who have or cannot tolerate nausea or vomiting. The possibility of complications from nausea and vomiting should be considered when administering TESLASCAN Injection to patients who cannot tolerate vomiting, who have reflux esophagitis (especially if it is increased in a supine position) or who cannot roll over to prevent aspiration. Of the 652 total patients in clinical studies, 17 vomited after TESLASCAN, 10 for less than 8 minutes, 5 for more than 2 hours, and 2 for an unrecorded time. Sixty-seven patients had nausea, 41 patients had nausea of 10 minutes or less, and 16 had nausea of 20 minutes or more. Ten patients had nausea of unknown duration.

PRECAUTIONS

GENERAL: THE DECISION TO USE CONTRAST ENHANCEMENT SHOULD INCLUDE A CONSIDERATION OF THE RISK OF THE DRUG, THE RISK OF THE PROCEDURE, THE EXPECTED BENEFIT OF THE IMAGE AND THE PATIENT'S UNDERLYING DISORDER. THE DECISION TO USE TESLASCAN INJECTION SHOULD BE BASED UPON CAREFUL EVALUATION OF CLINICAL DATA, OTHER RADIOLOGIC DATA AND THE RESULTS OF UNENHANCED MRI.

TESLASCAN Injection is cleared from the body partially by glomerular filtration and partially by hepatobiliary excretion (see CLINICAL PHARMACOLOGY section). Dose adjustments in renal or hepatic impairment have not been studied. Caution should be exercised in patients with impaired renal or impaired hepatobiliary function.

Diagnostic procedures involving the use of contrast agents should be conducted under supervision of a physician with the prerequisite training and a thorough knowledge of the procedure to be performed. Appropriate facilities should be available for coping with any complication of the procedure, as well as for emergency treatment of severe reactions to the contrast agent itself.

Although more lesions are generally visualized on contrast-enhanced images than on unenhanced images, lesions seen on unenhanced images may not all be seen on contrast-enhanced images. Possible causes include changes in imaging parameters, patient motion, misregistration, and effects of the contrast agent.

Repeat Procedures: The safety of repeated doses has not been studied. If the physician determines that imaging needs to be repeated, repeat images could be obtained up to 24 hours after the original injection without reinjection.

INFORMATION FOR PATIENTS

Patients receiving TESLASCAN should be instructed before injection to:

1. Inform their physician or health care provider if they are pregnant or nursing. (See Precautions - Pregnancy Category C section.)
2. Inform their physician or health care provider if they have a history of renal or hepatic disease or seizure.
3. Inform their physician or health care provider if they have a history of allergic reaction, immune system disorder, or reaction to other radiocontrast drugs.
4. Inform their physician or health care provider if they have abdominal pain, nausea, or vomiting.

Patients should be informed that:

1. TESLASCAN Injection has been prescribed for liver enhancement during MRI.
2. TESLASCAN Injection may cause nausea and vomiting.

DRUG INTERACTIONS

Drug interactions with other contrast agents and other drugs were not studied.

LABORATORY TEST INTERACTIONS

Transmetalation of manganese may occur. The extent to which this might affect laboratory assays of ferritin, iron, bilirubin, and zinc is not known.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY

Long-term animal studies have not been performed to evaluate the carcinogenic potential of TESLASCAN Injection. The results of the following genotoxicity assays were negative: bacterial reverse mutation assay, CHO/HGPRT forward mutation assay, CHO chromosome aberration assay, and the *in vivo* mouse micronucleus assay.

TESLASCAN was positive in an *in vitro* mouse BALB/c-3T3 assay, but negative when the test was repeated; the assays were performed with the same final concentrations of TESLASCAN in the culture medium. The contrast agent did not affect male or female rat reproductive performance when administered at daily doses up to 100 μmol/kg (3.33 times the clinical dose based on body surface area, 20 times based on body weight).

PREGNANCY CATEGORY C

TESLASCAN may cause harm to the fetus when administered to a pregnant woman. Manganese causes embryo toxicity and fetal toxicity in various animal species. In rats, TESLASCAN was teratogenic (increased incidence of skeletal malformations) and fetotoxic (decreased fetal body weight) after 12 consecutive daily injections with 10, 20 and 40 μmol/kg (days 6 through 17 of gestation). These doses did not produce toxicity in the dams. Adverse effects were not observed in fetal rats at doses of 5 μmol/kg/day (each daily dose was 0.16 of the single imaging dose based on body surface area and the same as the imaging dose based on body weight). In another developmental study of rats injected with TESLASCAN for 3 consecutive days, in 20-60% of the litters at the lowest daily dose tested (20 μmol/kg, each daily dose was 0.64 times the single imaging dose based on surface area; 4 times based on body weight) had skeletal abnormalities observed at each of the four 3-day intervals studied. In rabbits, TESLASCAN was embryotoxic and fetotoxic (increased post-implantation losses and resorptions, and decreased number of viable fetuses) following 13 consecutive daily doses of 40 and 60 μmol/kg on days 6 through 18 of gestation; these doses did not produce toxicity in the does. Adverse effects were not observed in fetal rabbits at doses of 20 μmol/kg (each daily dose was 1.33 times the single imaging dose based on body surface area, 4 times based on body weight).

Animal studies have shown that ^{54}Mn manganese crosses the placenta and locates in the fetus. At least 24 hours after injection, radioactivity is detected in liver and bones of the fetus. It has been reported that manganese enters nerve terminals, accumulates in nervous tissue and could be associated with neurotoxicity in fetuses.

Adequate and well controlled studies were not conducted in pregnant women. If TESLASCAN is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be told of the potential hazard to the fetus.

NURSING MOTHERS

The rate and extent to which manganese or mangafodipir is excreted in human milk after TESLASCAN Injection has not been studied. In the literature, there are reports that manganese is excreted in human milk. Also, in comparison to adults, neonates have higher intestinal absorption and bioavailability of manganese. The relationship between the bioavailability of manganese from human milk and subsequent toxicity in developing infants is not known. Because of the potential risk to nursing infants from manganese exposure, consideration should be given to temporarily discontinuing nursing to allow clearance of mangafodipir and manganese. (See CLINICAL PHARMACOLOGY - Elimination section.)

PEDIATRIC USE

Safety and effectiveness of TESLASCAN Injection in adolescents are expected to be the same as in adults.

Safety, effectiveness or pharmacokinetics of TESLASCAN Injection in pediatric patients below the age of 12 years have not been established.

ADVERSE REACTIONS

In clinical trials, a total of 637 subjects (57 healthy volunteers and 580 patients) with known or suspected liver lesions received the contrast agent at a dose of 5 μmol/kg. Of these subjects, there were 387 men and 250 women with a mean age of 56 years (19 to 86). There were 497 (78%) Caucasian, 72 (11%) Black, 32 (5%) Oriental, and 36 (6%) in other racial groups.

Of these 637 subjects, 481 (76%) reported at least one adverse event. In clinical trials, there were 4 deaths and 2 serious events. The serious events included prolonged vomiting in one patient. The deaths occurred in patients with advanced multisystem disease (hepatocellular carcinoma, esophageal variceal bleeding, sepsis, and pneumonia) and were attributed to the underlying disorders.

The most commonly noted adverse experiences were injection site discomfort 430 (67%), headache - 32 (5%), and any gastrointestinal event - 79 (12%). (See Table 5 for details.)

TABLE 5: ADVERSE EVENTS REPORTED IN ≥0.5% OF PATIENTS WHO RECEIVED TESLASCAN IN CLINICAL TRIALS

Patients Exposed to TESLASCAN	637
Patients with Any Adverse Event	481 (76%)
Patients with Any Injection Site Discomfort	430 (67%)
Gastrointestinal	79 (12%)
Nausea	67 (11%)
Vomiting	17 (3%)
Abdominal Pain	14 (2%)
Body as a Whole	25 (4%)
Headache	32 (5%)
Chest Pain	4 (0.6%)
Central & Peripheral Nervous System	48 (8%)
Dizziness	9 (1%)
Skin & Appendages	12 (2%)
Pruritus	7 (1%)

As with other contrast media, patients receiving TESLASCAN reported injection-associated discomfort. Overall 430 (67%) of the patients receiving TESLASCAN reported mild to moderate injection-associated discomfort. Of these, the discomfort was described as heat 266 (42%), flushing 234 (36%), pressure 26 (4%), pain 19 (3%), and cold 9 (1%).

The following selected adverse events occurred in <0.5% of the subjects. The majority (93%) of these adverse events were of mild to moderate intensity: chest pain, dizziness, hot flushes, hypersensitivity, hypertension, palpitation, pruritus, rash, taste perversion, urticaria.

In another 798 subjects who received the contrast agent in foreign clinical trials, similar types and rates of adverse events were reported.

OVERDOSAGE

Clinical consequences of overdosage with TESLASCAN Injection have not been reported. Treatment of an overdose is directed toward the support of all vital functions, and prompt institution of symptomatic therapy. The minimum lethal dose of mangafodipir trisodium when administered intravenously to mice as a bolus was >2000 μmol/kg (400 times the recommended human dose of 5 μmol/kg based on body weight and 17 times based on body surface area).

The dialyzability of TESLASCAN Injection and its metabolites has not been studied. Mangafodipir itself does not undergo protein binding *in vitro*; however, manganese (II) and manganese (III) are known to bind to plasma proteins *in vitro*.

DOSAGE AND ADMINISTRATION

TESLASCAN Injection should be administered as a peripheral intravenous injection at a dose of 5 μmol/kg (0.1 mL/kg) over approximately one minute. The maximum dose should not exceed 15 mL. (See the Dosage Chart.)

TESLASCAN Injection should be drawn into the syringe and administered using sterile technique. If nondisposable equipment is used, scrupulous care should be taken to prevent residual contamination with traces of cleansing agents. Unused portions of the drug must be discarded.

Imaging can begin within minutes after TESLASCAN Injection. If it is determined that imaging needs to be repeated, repeat images could be obtained up to 24 hours after the original injection without reinjection. The safety of repeat doses has not been studied. (See Pharmacodynamics and Clinical Trials.)

Exhibit

1

DOSAGE CHART

BODY WEIGHT kg	BODY WEIGHT lb	VOLUME (mL)
40	88	4
50	110	5
60	132	6
70	154	7
80	176	8
90	198	9
100	220	10
110	242	11
120	264	12
150	330	15

Dose should not exceed 15 mL.

Other drugs should not be physically mixed with contrast agents because of the potential for chemical incompatibility. If the injection is made through tubing, the injection should be followed by a 5 mL flush with 0.9% sodium chloride.

Parenteral products should be inspected visually for particulate matter and discoloration prior to administration. Do not use if the solution is other than clear yellow or if particulate matter is present.

HOW SUPPLIED

10 mL vial, box of 5, NDC 0407-0695-10

STORAGE

Store in the original, unopened container between 15°C and 30°C (59°F to 86°F). **Protect from freezing.** Do not use product if it has been frozen. Freezing may compromise the package integrity.

Store vials on their side in the original carton. **Do not store the vials upright.** Upright storage may cause oxidation or discoloration.

Caution: Federal law prohibits dispensing without prescription.

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CERTIFICATE OF CORRECTION

PATENT NO. : 4,933,456

DATED : June 12, 1990

INVENTOR(S) : Scott M. Rocklage et al.

It is certified that error appears in the above-indentified patent and that said Letters Patent is hereby corrected as shown below:

Col. 25, lines 55-58 (claim 1), immediately following the words "R is hydrogen or"

change the formula: " $CH\overset{O}{\overset{\|}{C}}R_5$ " to -- $CH_2\overset{O}{\overset{\|}{C}}R_5$ -- ; and

Col. 25, lines 60-63 (claim 1), immediately following the words "R_1 is hydrogen or"

change the formula: " $CH\overset{O}{\overset{\|}{C}}R_6$ " to -- $CH_2\overset{O}{\overset{\|}{C}}R_6$ -- .

EXHIBIT 2

United States Patent [19]

Rocklage et al.

[11] **Patent Number: 4,933,456**

[45] **Date of Patent: Jun. 12, 1990**

[54] **DIPYRIDOXYL PHOSPHATE NMRI CONTRAST AGENTS**

[75] Inventors: **Scott M. Rocklage, Saratoga; Steven C. Quay, Los Altos Hills, both of Calif.**

[73] Assignee: **Salutar, Inc., Sunnyvale, Calif.**

[21] Appl. No.: **47,614**

[22] Filed: **May 8, 1987**

[51] Int. Cl.[5] C07F 1/02; C07F 3/04; C07F 13/00; C07F 9/58

[52] U.S. Cl. 546/5; 544/109; 424/1.1; 546/24; 546/261

[58] Field of Search 546/261, 24, 5; 544/109

[56] **References Cited**

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4,489,053	12/1984	Azuma et al.	424/1.1
4,637,929	1/1987	Quay	424/9
4,647,447	3/1987	Gries et al.	424/9
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Taliaferro, C. et al.; "NMR Investigation of Protonation Sites et seq."; Inorg. Chem.; 24:2408–2413 (1985).

Green, M. et al.; "Evaluation of PLED as a Chelating Ligand et seq."; Int. J. Nucl. Mec. Biol.; 12(5):381–386 (1985).

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Rocklage et al.; "Manganese (II) N,N'-Dipyridoxylethylenediamine-N,N'–et seq"; Inorganic Chemistry; 1989, 2,477.

Primary Examiner—Alan L. Rotman

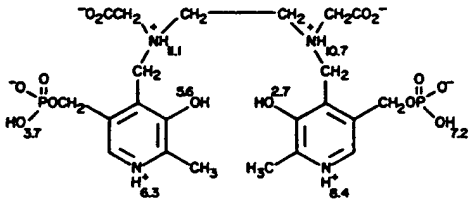
Attorney, Agent, or Firm—Lyon & Lyon

[57] **ABSTRACT**

N,N'-bis-(pyridoxal-5-phosphate)-alkylenediamine-N,N'-diacetic acids, N,N'-bis-(pyridoxal-5-phosphate)-1,2-cycloalkylenediamine-N,N'-diacetic acids, and N,N'-bis-(pyridoxal-5-phosphate)-1,2-arylenediamine-N,N'-diacetic acids, the corresponding monophosphate compounds and monoacetic acid compounds, and their salts and esters form stable, highly soluble chelates with paramagnetic metal ions, and are highly effective NMRI contrast agents. Preferred contrast agents are paramagnetic ion chelates of N,N'-bis-(pyridoxal-5-phosphate)ethylene-diamine-N,N'-diacetic acid, N,N'-bis-(pyridoxal-5-phosphate)trans-1,2-cyclohexylenediamine-N,N'-diacetic acid, N,N'-bis-(pyridoxal-5-phosphate)trans-1,2-arylenediamine-N,N'-diacetic acid, and the soluble calcium salts thereof.

Novel intermediates for forming these compounds are N,N'-bis(pyridoxal-5-phosphate)alkylenediimines, N,N'-bis(pyridoxal-5-phosphate)alkylenediamines, N,N'-bis(pyridoxal-5-phosphate)-1,2-cycloalkylenediimines, N,N'-bis(pyridoxal-5-phosphate)-1,2-cycloalkylenediamines, N,N'-bis(pyridoxal-5-phosphate(-1,2-arylenediamines, and the corresponding monophosphate compounds.

18 Claims, 1 Drawing Sheet



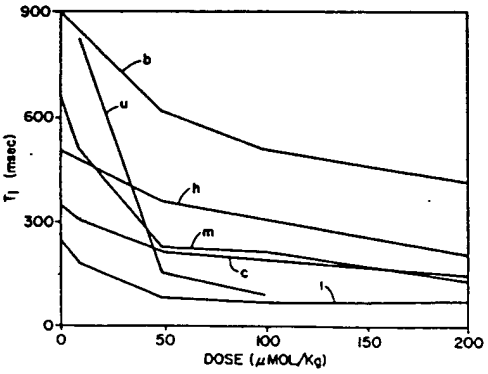


EXHIBIT 2

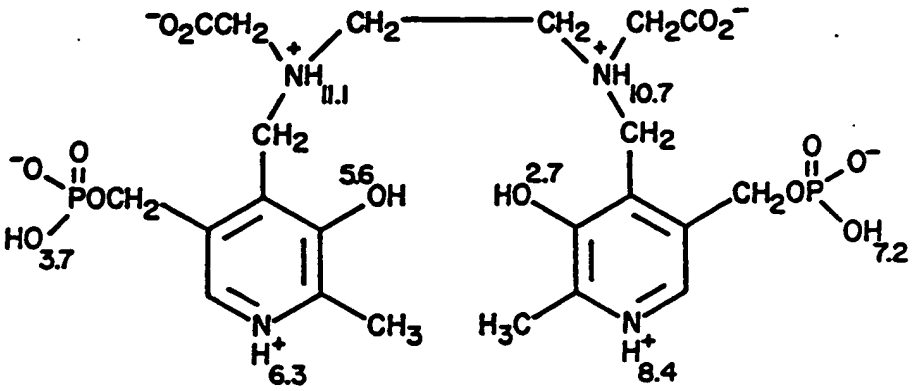

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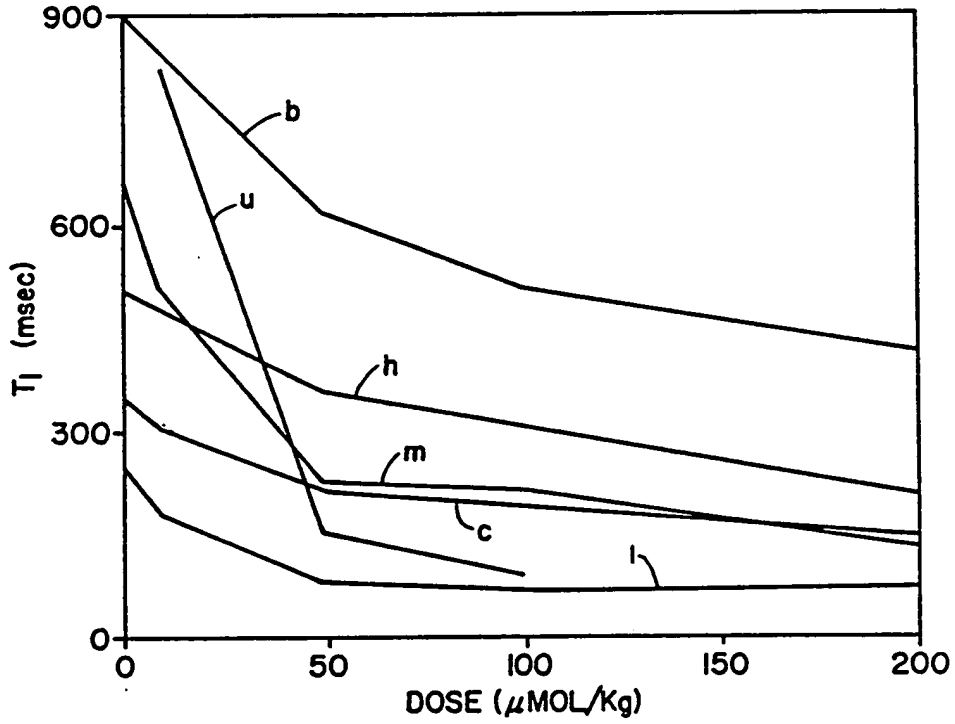
FIG._1.


900
600
300
0
T_1 (msec)
b
u
h
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200
DOSE (μMOL/Kg)

FIG._2.

DIPYRIDOXYL PHOSPHATE NMRI CONTRAST AGENTS

FIELD OF THE INVENTION

This invention relates to novel compounds which form highly stable chelates with metal ions and which are useful as metal ion carriers for in vivo medical applications. In particular, this invention is directed to novel dipyridoxyl compounds which form highly stable chelates with polyvalent metal ions, the preparation of the compounds and chelates thereof with polyvalent ions and particularly paramagnetic ions, and the use of the paramagnetic chelates as contrast agents in nuclear magnetic resonance imagery (NMRI).

BACKGROUND OF THE INVENTION

Traditionally, chelates have been used to administer poorly soluble salts in medicine and as antidotes for detoxification in cases of heavy metal or heavy metal isotope poisoning. Chelates have also been used to deliver radioisotopes to areas of the body for imaging and radiation therapy. Most recently, chelates with paramagnetic contrast agents have been reported for use with NMRI.

Paramagnetic metal ions are frequently toxic in the concentrations required for use in NMRI, and introducing them into the body in the form of chelates renders them more physiologically acceptable. This requires that a chelate be able to hold the metal ion tightly in the chelate structure, that is, the formation constant for the chelate must be very large at physiological pH. The paramagnetic metal chelate must also be sufficiently soluble to permit administration of quantities required for imaging in reasonable volumes. Usual routes of administration are orally, intravenously and by enema.

The chelating agent must form a stable chelate with those paramagnetic metals which present a hazard to the body if released during use. Paramagnetic metals which are naturally present in the body are preferred. The chelate forming agent (ligand) must be capable of forming a chelate with a selected paramagnetic material without altering the metal's oxidation state or otherwise reducing its chemical stability.

Since the role of the paramagnetic metal in increasing contrast in NMRI imaging involves reducing the spin-lattice spin relaxation time T_1 and the spin-spin relaxation time T_2, the chelate structure must hold the metal ion tightly while permitting contact of the metal ion with protons in water molecules.

This invention provides a novel, superior chelating agent and metal complexes therewith which meet the above objectives.

DESCRIPTION OF THE PRIOR ART

A summary of the history and state of the art of contrast agents for NMRI is presented by Valk, J. et al, *Basic Principles of Nuclear Magnetic Resonance Imaging*. New York: Elsevier, pp 109–114 (1985). The Valk et al publication also describes the imaging equipment and methods for NMRI, and the entire contents of the Valk et al publication are hereby incorporated by reference in their entirety. Chelates with ethylenediaminetetraacetic acid (EDTA) and diethylaminetriaminepentaacetic acid (DTPA) are described. Toxicity problems were reduced by seeking less toxic metal ions such as iron and gadolinium in a complex of gadolinium-DTPA chelate-meglumine. Gadolinium, however, is not naturally present in the body and long term toxicity studies have not been completed. Paramagnetic materials listed in this publication include molecules with unpaired electrons: nitric oxide (NO); nitrogen dioxide (NO_2); and molecular oxygen (O_2). Also included are ions with unpaired electrons, that is ions from the "transition series". Listed ions include Mn^{2+}, Mn^{3+}, Fe^{2+}, Fe^{3+}, Ni^{2+}, Cr^{2+}, Cu^{2+}, the lanthanide series including gadolinium and europium, and nitroxide stable free radicals (NSFR) such as pyrrolidine NSFR and piperidine NSFR. Toxicity problems are indicated to present a major problem with many paramagnetic materials.

Use of alkylenediamine chelates with a variety of paramagnetic ions are described in U.S. Pat. No. 4,647,447. Ferrioxamine-paramagnetic contrast agents are described in U.S. Pat. No. 4,637,929. Manganese(II) is listed as a suitable paramagnetic metal ion for use with polysaccharide derivatives of a variety of chelating compounds including EDTA, DTPA and aminoethyl diphosphonate in PCT application publication no. WO85/05554 (Application No. PCT/GB85/00234). Stable radioactive diagnostics agents containing ^{99m}Tc chelated with N-pyridoxal-alpha-aminoacids or a pyridoxal salt are disclosed in U.S. Pat. Nos. 4,313,928, 4,440,739, and 4,489,053.

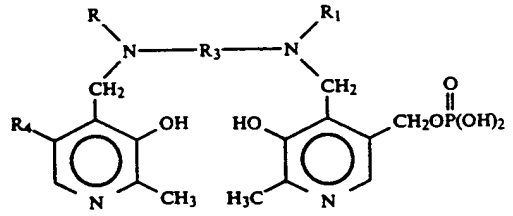
Taliaferro, C. et al in "New multidentate ligands. 22. N,N'-dipyridoxyethylenediamine-N,N'-diacetic acid: a new chelating ligand for trivalent metal ions", *Inorg. Chem.* 23:1188–1192 (1984) describe development of N,N,-dipyridoxyethylenediamine-N,N,-diacetic acid (PLED) as a chelating compound for trivalent metal ions. Other chelating compounds described are the Fe(III) chelates of N,N'-ethylenebis-2-(o-hydroxyphenyl)glycine (EHPG) and N,N'-bis(1-hydroxybenzyl)ethylenediamine-N,N'-diacetic acid (HBED). Properties of chelates of PLED, HBED, EHPG and EDTA with ions of copper, nickel, cobalt, zinc, iron, indium and gallium are compared. Investigation of the structure of PLED is reported by Taliaferro, C. et al, *Inorg. Chem.* 24:2408–2413 (1985). Green, M. et al, *Int. J. Nucl. Med. Biol.* 12(5):381–386 (1985) report their evaluation of PLED as a chelating ligand for the preparation of gallium and indium radiopharmaceuticals, and summarize properties of PLED chelates with Ga(III), In-(III), and Fe(III).

Because the compounds of this invention have an aromatic hydroxy group, their value as chelating agents for manganese(II) ions would not be expected; such aromatic hydroxy groups would be expected to react with the manganese(II) ion as an oxidant in the usual way, oxidizing the manganese(II) ion to a higher valence. Frost, et al, *J. Am. Chem. Soc.* 80:530 (1958) report the formation of Mn(II) chelates of EHPG at low pH, but found that attempts to prepare stable manganese(II) complexes with EHPG at higher pH's (above pH 5) was futile as the manganese(II) ion was irreversibly oxidized. This oxidation occurred even under inert atmospheres, and the writers concluded that the oxidation occurred at the expense of the ligand or solvent. Anderegg, G. et al, *Helv. Chim. Acta.* 47:1067 (1964) found the high stability of the Fe(III) chelate of EHPG was due to the high affinity of the Fe(III) ion for the two phenolate groups present in the ionized ligand. L'Eplathenier, F. et al, *J. Am. Chem. Soc.* 89:837 (1967) describes studies of HBED involving acid titrations of HBED in the presence of a variety of metal ions, including manganese(II). No manganese chelate was isolated,

and the manganese products were not characterized. Based on subsequent work by Patch et al, *Inorg. Chem.* 21(8):2972–2977 (1982), it is clear that the manganese(II) ion was oxidized by the phenolic ligand during the titrations of L'Eplathenier et al. Patch et al prepared a Mn(III) complex by reacting Mn(II) salts with EHPG, and concluded the reaction involved the oxidation of the ligand in an irreversible reaction. The ability to maintain Mn(III) in the +3 oxidation state was said to be a unique characteristic of the EHPG molecule. U.S. Pat. No. 3,632,637 describes phenolic chelating agents such as N,N-di(o-hydroxylbenzyl)-ethylenediamine-N,N'-diacetic acid and their use in chelating trivalent and tetravalent metals. These agents are usually stable in the presence of aromatic hydroxy groups. No use of a compound with an aromatic hydroxy group as a chelating agent for manganese(II) ions is disclosed in these references, confirming the general knowledge about the oxidizing properties of the aromatic hydroxy group on manganese compounds, in particular manganese(II) ions.

SUMMARY OF THE INVENTION

The novel chelate forming compounds of this invention are shown in Formula I.

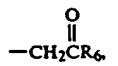


(I)

wherein

R is hydrogen or

R_1 is hydrogen or



and one of R and R_1 is other than hydrogen;

R_3 is alkylene having from 1 to 8 carbons, 1,2-cycloalkylene having from 5 to 8 carbons, or 1,2-arylene having from 6 to 10 carbons, and

R_4 is hydrogen, alkyl having from 1 to 6 carbons or

R_5 and R_6 are each, individually, hydroxy, alkoxy having from 1 to 18 carbons, hydroxy-substituted alkoxy having from 1 to 18 carbons, amino or alkylamido having from 1 to 18 carbons.

The phosphate group mono and diesters with mono and polyhydric alkanols having from 1 to 18 carbons, or alkylamino alcohols, each having from 1 to 18 carbons, and the salts of the above compounds are included within the scope of this invention.

Also included in this invention are the chelates of the compounds of Formula I and salts and esters thereof with metal ions, preferably paramagnetic metal ions having atomic numbers of from 21–29, 42, 44 and 58–70, and optimally manganese(II), and their use as imaging agents.

The novel intermediate compounds from which the compounds of Formula I are prepared are also included within the compounds of this invention.

BRIEF DESCRIPTION OF THE DRAWING

FIG. 1 shows a structural formula of a species of N,N'-bis(pyridoxal-5-phosphate)ethylenediamine-N,N'-diacetic acid, showing the dissociation constants, pK's, as assigned to the protonation sites described in Example 11.

FIG. 2 is a graph showing the relationship between dosage and relaxivity using the Mn(DPDP) compound of this invention based on the data shown in Example 9.

DETAILED DESCRIPTION OF THE INVENTION

The novel chelate forming compounds of this invention are shown in Formula I. The pharmaceutically acceptable water-soluble compatible salts of the compounds of Formula I and phosphate group esters of the compounds of Formula I with polyhydric alcohols, aliphatic alcohols, or alkylamino alcohols, each having from 1 to 18 carbons, and the chelates thereof are also included within the compounds of this invention.

In Formula I, R_5 and R_6 are preferably each individually hydroxy, alkoxy having from 1 to 8 carbons, ethylene glycol, glycerol, amino or alkylamido having from 1 to 8 carbons. Optimally, R_5 and R_6 are hydroxy and the salts thereof.

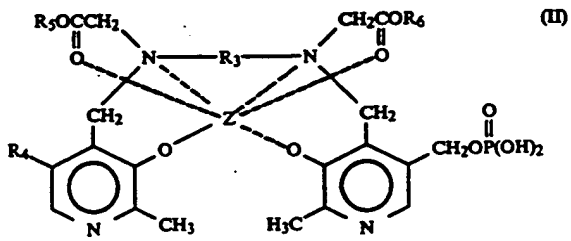
The term "alkyl" and "alkylene", as used herein, include both straight and branch-chained, saturated and unsaturated hydrocarbons. The term "1,2-cycloalkylene" includes both cis and trans cycloalkyl groups and alkyl substituted cycloalkylene groups bonded at the 1,2-positions to respective nitrogen atoms and alkyl substituted derivatives thereof having from 5 to 8 carbons. The term "1,2-arylene" includes phenyl and naphthyl groups bonded at the 1,2-positions to respective nitrogen atoms and alkyl substituted derivatives thereof, having from 6 to 10 carbons.

The compound, N,N'-bis-(pyridoxal-5-phosphate)-ethylenediamine-N,N'-diacetic acid or N,N'-bis(3-hydroxy-2-methyl-5-phosphonomethyl-4-pyridylmethyl)ethylenediamine-N,N'-diacetic acid, is referred to hereinafter as DPDP, and the Manganese(II) chelate is referred to hereinafter as Mn(DPDP).

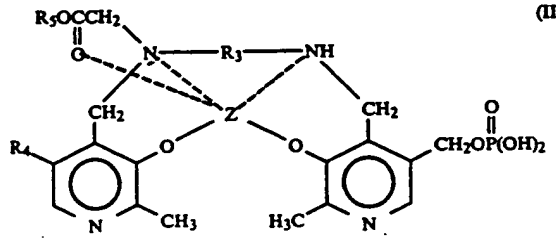
The dicarbonyl compound of Formula I, when R_5 and R_6 are hydroxy and R_3 is ethylene, is DPDP. DPDP has the dissociation constants for the protonation sites shown in FIG. 1. As described in Example 11, at pH of 3 and above, the ligand is anionic and possesses deprotonated metal binding sites, both important criteria for metal chelating agents.

CHELATES

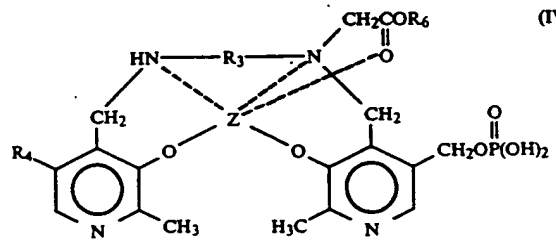
The chelates of this invention are chelates of the compounds of Formula I with metal ions. The chelates can be represented by Formulas II, III or IV.



(II)



(III)



(IV)

In Formulas II, III and IV, Z represents a metal ion and R_3, R_4, R_5 and R_6 are the same as described with respect to the compounds of Formula I. The dotted lines in the figure represent the dative bonding between the oxygen and nitrogen atoms and the metal ion. One of the acetyl groups in Formula II is below the plane of the aromatic pyridine rings and the other acetyl group is above the plane of the aromatic pyridine rings, so the metal ion is tightly held within the interior of the chelate salt complex with the dicarboxy embodiments of this invention. Also included in the chelates of this invention are the pharmaceutically acceptable water-soluble compatible salts, and carboxylic and phosphate group esters with hydroxy-substituted alkanols, alkanols, or alkylamino alcohols, each having from 1 to 18 carbons, of the compounds of Formulas II, III, and IV.

For use as a medium for NMRI analysis, the central ion of the complex chelate salt must be paramagnetic, and preferably is a divalent or trivalent ion of elements with an atomic number of 21 to 29, 42, 44 and 58 to 70. Suitable ions include chromium(III), manganese(II), iron(III), iron(II), cobalt(II), nickel(II), copper(II), praseodymium(III), neodymium(III), samarium(III), ytterbium(III). Gadolinium(III), terbium(III), dysprosium(III), holmium(III) and erbium(III) are sometimes preferred because of their strong magnetic moments and chemical stability, but because they are not normally present in the body, their long term biological effects are unknown.

With the novel chelate forming compounds of Formula I, chelates of manganese(II) are preferred. Relatively few manganese(II) chelate compounds are known, and only a fraction of these have been characterized i.e., by single crystal X-ray diffraction. Most of the structurally characterized Mn(II) complexes have various mono and bidentate ligands coordinating to the metal center. The Mn(II) complexes of Formulas II, II and III, and the Mn(II) complexes with PLED and the corresponding 1,2-cycloalkylene and 1,2-arylene compounds described in our co-pending, concurrently filed application U.S. Ser. No. 47,584 filed May 8, 1987 titled Manganese(II) Chelate Contrast Agents and Methods are the first Mn(II) complexes with a high affinity hexadentate ligand. This configuration provides a more stable and effective form for introducing manganese(II) into the body as a NMRI contrast medium.

The manganese(II) complex of Formula II (R_5 and R_6=hydroxy; R_3=ethylene), Mn(DPDP), was studied potentiometrically from pH 11.1 to 2.0. The data obtained was analyzed using a model consisting of three one proton steps and one two proton step. Refinement yielded equilibrium constants with calculated e.s.d.'s (log K) of less than 0.02. The log K_f (formation constant) for Mn(DPDP) was calculated to be 14.8 and is identical to that of the manganese chelate of N,N'-bis(2-hydroxybenzyl)ethylenediamine-N,N'-diacetic acid (HBED) reported by L'Eplathenier, F. et al (supra). The titration data indicates that Mn(DPDP) begins to demetallate as the pH drops below 4.5. At physiological pH, however, the Mn(II) ion is quantitatively bound to the chelating agent, stabilized at the +2 valence.

The chelate forming compounds of this invention are also suitable for forming chelate salts of other metals intended for X-ray diagnosis. In general, these are the elements of an atomic number which is sufficiently high to efficiently absorb X-rays. Diagnostic media containing a physiologically well tolerated chelate salt with central ions of elements with atomic numbers of 57 to 83 are suitable for this purpose. Included in this group are lanthanum(III), gold(III), lead(II), and bismuth(III).

All of the chelates according to this invention useful for NMRI and X-ray analysis are also suitable for use in ultrasonic diagnosis.

The elements of the above-listed atomic numbers which form the central ion or ions of the physiologically well tolerated chelate salt, must not be radioactive for the intended use of the diagnostic medium for X-ray diagnosis and NMRI. Radioactive metal chelates of the compounds of Formula I are described in our U.S. Ser. No. 47,616 filed May 8, 1987, and U.S. Pat. No. 4,842,845, issued June 27, 1989 titled Dipyridoxyl Phosphate Radioactive Metal Chelates.

For purposes of clarity, the chelates of this invention will be described hereinafter in terms of paramagnetic ions suitable for use in NMRI analysis. However, this is for purposes of clarity of explanation and not by way of limitation, and chelates of all of the above metal ions are included within the scope of this invention.

If not all of the active hydrogen atoms of the chelates are substituted by the central paramagnetic ion, the solubility of the chelate is increased if the remaining hydrogen atoms are substituted with physiologically biocompatible cations of inorganic and/or organic bases or amino acids. For example, the lithium ion, the potassium ion, the sodium ion and especially the calcium ion are suitable inorganic cations. Suitable cations of organic bases include, for example, ethanolamine, diethanolamine, morpholine, glucamine, N,N-dimethylglucamine, and N-methylglucamine. Lysine, arginine or orithine are suitable as cations of amino acids, as generally are those of other basic naturally occurring acids.

The preferred calcium salts have calcium ion to chelating molecule mole ratios of from 0.05 to 1.0, the optimum mole ratios being with the range of from 0.1 to 0.5. At mole ratios of calcium ion to chelate molecule

above 1.0, the chelate tends to become insoluble. The soluble calcium salts are most physiologically acceptable since they do not significantly disturb the concentration of free calcium ions in the patient's system.

The chelates according to this invention are formed from the chelate forming compounds of Formula I by conventional procedures known in the art. In general, these processes involve dissolving or suspending the metal oxide or metal salt (for example, nitrate, chloride or sulfate) of an element with an atomic number of 21 to 29, 42, 44 or 57 to 83 (for example, oxides or salts of Mn^{+2}, Cr^{+3}, Fe^{+2}, Fe^{+3}, Co^{+3}, Ni^{+2}, Cu^{+2}, Pr^{+3}, Nd^{+3}, Sm^{+3}, Yb^{+3}, Gd^{+3}, Tb^{+3}, Dy^{+3}, Ho^{+3}, or Er^{+3}) in water or a lower alcohol such as methanol, ethanol or isopropanol. To this solution or suspension is added an equimolar amount of the chelating acid in water or a lower alcohol, and the mixture is stirred, if necessary, with heating moderately or to the boiling point, until the reaction is completed. If the chelate salt formed is insoluble in the solvent used, the reaction product is isolated by filtering. If it is soluble, the reaction product is isolated by evaporating the solvent to dryness, for example, by spray drying or lyophilizing.

If acid groups such as the phosphoric acid groups are still present in the resulting chelate, it is advantageous to convert the acidic chelate salt into a neutral chelate salt by reaction with inorganic and/or organic bases or amino acids, which form physiologically biocompatible cations, and to isolate them. This is often unavoidable since the dissociation of the chelate salt is moved toward neutrality to such an extent by a shift in the pH value during the preparation that only in this way is the isolation of homogeneous products or at least their purification made possible. Production is advantageously performed with organic bases or basic amino acids. It can also be advantageous, however, to perform the neutralization by means of inorganic bases (hydroxides, carbonates or bicarbonates) of sodium, potassium or lithium.

To produce the neutral salts, enough of the desired base can be added to the acid chelate salts in an aqueous solution or suspension that the point of neutrality is reached. The resulting solution can then be concentrated to dryness in vacuo. It is often advantageous to precipitate the neutral salts by adding a solvent miscible with water, for example, lower alcohols (methyl, ethyl, isopropyl alcohols, etc.), lower ketones (acetone, etc.), polar ethers (tetrahydrofuran, 1,2-dimethoxyethane, etc.) and thus obtain crystals that isolate easily and purify well. It has been found particularly advantageous to add the desired bases to the reaction mixture even during chelating and thus eliminate a process stage. Other conventional purification procedures such as column chromatography can be used.

Since the chelate salts of Formulas II, III and IV contain a plurality of acid groups, it is possible to produce neutral mixed salts which contain both inorganic and organic physiologically biocompatible cations as counterions. This can be done, for example, by reacting the complexing acids in an aqueous suspension or solution with the oxide or salt of the element supplying the central ion or less than the full amount of an organic base necessary for neutralization, e.g., half, isolating the chelate salt that is formed, purifying it, if desired, and then adding it to the amount of inorganic base necessary for complete neutralization. The sequence of adding the bases can be reversed.

The carboxylic and phosphoric acid groups of the chelating agents can also be neutralized by esterification to prepare carboxylate and phosphate esters. Such esters can be prepared by conventional procedures known in the art, for example, from the corresponding alcohols. Suitable esters include, for example, esters of straight or branch-chained alkanol groups having from 1 to 18 carbons, mono and polyhydric alkyl amino alcohols having from 1 to 18 carbons and preferably from 1 to 6 carbons such as serinol or diethanolamine, and polyhydric alcohols having from 1 to 18 and preferably from 1 to 6 carbons such as ethylene glycol or glycerol.

The diagnostic media for administration is formed using physiologically acceptable media in a manner fully within the skill of the art. For example, the chelate salts, optionally with the addition of pharmaceutically acceptable excipients, are suspended or dissolved in an aqueous medium, and then the solution or suspension is sterilized. Suitable additives include, for example, physiologically biocompatible buffers (as, for example, tromethamine hydrochloride), slight additions of other chelating agents (as for example, diethylenetriaminepentacetic acid) or, optimally, calcium salts (for example, calcium chloride, calcium ascorbate, calcium gluconate or calcium lactate).

Alternatively, the diagnostic media according to this invention can be produced without isolating the chelate salts. In this case, special care must be taken to perform the chelating so that the salts and salt solutions according to the invention are essentially free of unchelated, potentially toxic metal ions. This can be assured, for example, using color indicators such as xylenol orange to control titrations during the production process. A purification of the isolated salt chelate can also be employed as a final safety measure.

If suspensions of the chelate salts in water or physiological salt solutions are desired for oral administration, a small amount of soluble chelate salt can be mixed with one or more of the inactive ingredients traditionally present in oral solutions such as surfactants, aromatics for flavoring and the like.

The most preferred mode for administering paramagnetic metal chelates as contrast agents for NMRI analysis is by intravenous administration. Intraveneous solutions must be sterile, free from physiologically unacceptable agents, and should be isotonic or iso-osmotic to minimize irritation or other adverse effects upon administration. Suitable vehicles are aqueous vehicles customarily used for administering parenteral solutions such as Sodium Chloride Injection, Ringer's Injection, Dextrose Injection, Dextrose and Sodium Chloride Injection, Lactated Ringer's Injection, and other solutions such as are described in Remington's Pharmaceutical Sciences. 15th Ed., Easton: Mack Publishing Co. pp 1405–1412 and 1461–1487 (1975) and The National Formulary XIV. 14th Ed. Washington: American Pharmaceutical Association (1975), the contents of which are hereby incorporated by reference. The solutions can contain preservatives, antimicrobial agents, buffers and antioxidants conventionally used in parenteral solutions, selecting excipients and other additives which are compatible with the chelates and which will not interfere with the manufacture, storage or use of the products.

The diagnostic media according to this invention can contain from 0.001 to 5.0 moles per liter and preferably from 0.1 to 0.5 moles per liter of the chelate salt.

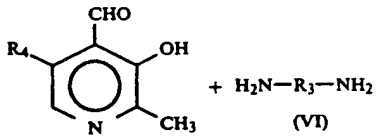
The chelates of this invention are administered to patients for imaging in amounts which are sufficient to yield the desired contrast. Generally, dosages of from 0.001 to 5.0 mmoles of contrast agent per kilogram of patient body weight are effective to achieve reduction of relaxivity rates. The preferred dosages for most NMRI applications are from 0.02 to 0.5 mmoles of contrast agent per kilogram of patient body weight.

Methods for applying the contrast agents to improve NMRI images, equipment and operating procedures are described by Valk, J. et al, supra. The contrast agents can be used orally and intravenously.

In a novel NMRI application, the contrast agents can be introduced into the cervix, uterus and fallopian tubes. NMR imaging can then be performed to detect causes of infertility such as obstructions or imperfections in the internal surface of the fallopian tubes which might interfere with the movement of the fertilized ovum.

CHELATE FORMING COMPOUNDS

The compounds of Formula I can be formed by reacting the corresponding pyridoxal 5-phosphate (3-hydroxy-2-methyl-5-phosphonomethyl-4-pyridinecarboxyaldehyde) represented by Formula V with a diamine represented by Formula VI.

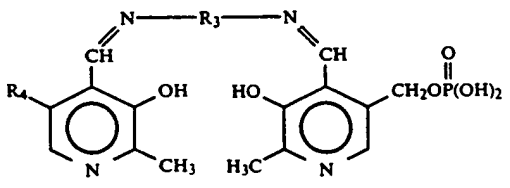


(V) (VI)

In the compounds of Formula V and VI, R_3 and R_4 are as defined with respect to Formula I. Pyridoxyl 5-phosphate, pyridoxal, and the other compounds of Formula V, and the alkylenediamine, cycloalkylenediamine and arylene reactants of Formula VI are well known compounds readily available from commercial sources, and they can be readily synthesized by well known procedures fully within the skill of the art.

The reaction of the amino groups of the compounds of Formula VI with the aldehyde group of the compounds of Formula V can be carried out in an alcohol such as methanol at a temperature within the range of from 0° to 60° C. The diimines formed are represented by Formula VII.

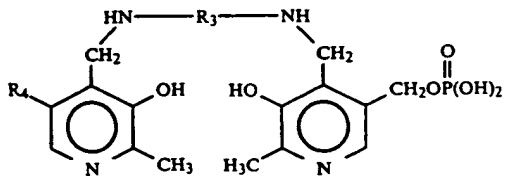
(VII)



In the compounds of Formula VII, R_3 and R_4 are the same as described with respect to the compounds of Formula I. For the manufacture of compounds wherein R_4 is a phosphonomethyl group, i.e., the 5-(N-(3-hydroxy-2-methyl-5-phosponomethyl-4-pyridyl)-methylideneaminoalkyleneiminomethyl)-2-hydroxy-3-methyl-5-pyridylmethylphosphoric acids, 5-(N-(3-hydroxy-2-methyl-5-phosponomethyl-4-pyridyl)-methylideneamino-1,2-cycloalkyleneiminomethyl)-2-hydroxy-3-methyl-5-pyridylmethyl phosphoric acids, and 5-(N-(3-hydroxy-2-methyl-5-phosponomethyl-4-pyridyl)-methylideneamino-1,2-aryleneiminomethyl)-2-hydroxy-3-methyl-5-pyridylmethyl phosphoric acids of Formula VII, a diamine of Formula VI is reacted with two molar equivalents of an aldehyde of Formula V having the 5-phosphonomethyl group such as pyridoxyl 5-phosphate. For preparation of compounds of Formula VII wherein R_4 is other than a phosphonomethyl group, the diamine of Formula VI is first reacted with only one molar equivalent of an aldehyde of Formula V having the 5-phosphonomethyl group, and the mono-phosphonomethyl reaction product is reacted with one molar equivalent of a compound of Formula V having the desired R_4 group, such as a 5-hydroxymethyl group, i.e., pyridoxal. The reverse order of reaction can also be used. The reaction products of Formula VII are insoluble in the alcohol and can be isolated by filtration.

The compounds of Formula VII are then hydrogenated by conventional procedures using a palladium or platinum catalyst to yield the diamines of Formula VIII.

(VIII)



In the compounds of Formula VIII, R_3 and R_4 are the same as described with respect to the compounds of Formula IV. The 5-(N-(3-hydroxy-2-methyl-5-phospono-methyl-4-pyridyl)-methylaminoalkyleneaminomethyl)-2-hydroxy-3-methyl-5-pyridylmethylphosphoric acids, 5-(N-(3-hydroxy-2-methyl-5-phosponomethyl-4-pyridyl)-methylamino-1,2cycloalkyleneaminomethyl)-2-hydroxy-3-methyl-5-pyridylmethyl phosphoric acids, 5-(N-(3-hydroxy-2-methyl-5-phosponomethyl-4-pyridyl)methylamino-1,2-cycloaryleneaminomethyl)-2-hydroxy-3-methyl-5-pyridylmethyl phosphoric acids, and the monophosphonomethyl compounds of Formula VIII can be left in solution or isolated as crystalline solids.

The compounds of Formula I are prepared by reacting the diamines of Formula VIII with a haloacetic acid such as bromoacetic acid, the molar ratio of the bromoacetic acid to diamine determining whether one or both of the amines are conjugated with the acetic acid groups. The N,N'-bis(3-hydroxy-2-methyl-5-phosphonomethyl-4-pyridyl-methyl)alkylenediamine-N,N'-diacetic acids, N,N'-bis(3-hydroxy-2-methyl-5-phosphonomethyl-4-pyridyl-methyl)-1,2-cycloalkylenediamine-N,N'-diacetic acids, N,N'-bis(3-hydroxy-2-methyl-5-phosphonomethyl-4-pyridyl-methyl)-1,2-arylenediamine-N,N'-diacetic acids, N,N'-bis(3-hydroxy-2-methyl-5-phosphonomethyl-4-pyridylmethyl)alkylenediamine-N-acetic acids, N,N'-bis(3-hydroxy-2-methyl-5-phosphonomethyl-4-pyridyl-methyl)-1,2-cycloalkylenediamine-N-acetic acids, and N,N'-bis(3-hydroxy-2-methyl-5-phosphonomethyl-4-pyridyl-methyl)-1,2-arylenediamine-N-acetic acids of Formula I are then isolated and purified by conventional procedures such as recrystallization or anion exchange chromatography.

The carboxylic acid esters and amides can be formed by conventional procedures reacting the carboxylic acids with alkanols having from 1 to 18 carbons, hy-

droxy-substituted alkanols having from 1 to 18 carbons, ammonia, and alkylamines having from 1 to 18 carbons.

This invention is further illustrated by the following specific but non-limiting examples. Temperatures are given in degrees centigrade and concentrations as weight percents unless otherwise specified. Procedures which are constructively reduced to practice herein are described in the present tense, and procedures which have been carried out in the laboratory are set forth in the past tense.

EXAMPLE 1

N,N'-bis(pyridoxal-5-phosphate)ethylenediimine

A 265.2 gm (1 mole) quantity of pyridoxal-5-phosphate (Chemical Dynamics Corp., South Plainfield, N.J.) was slurried in one liter of methanol, and 400 ml of 5M NaOH was added. When the solution was homogeneous, 34.2 ml of 1,2-diaminoethane (Aldrich Chem. Co.) was added rapidly with vigorous stirring. The imine product sodium N,N'-bis(pyridoxal-5-phosphate)ethylenediimine or sodium 5-(N-(3-hydroxy-2-methyl-5-phosponomethyl-4-pyridyl)methylideneaminoethyleneiminomethyl)-2-hydroxy-3-methyl-5-pyridylmethylphosphate was stirred for 1 hr, 400 ml of diethyl ether was added, and the slurry was filtered. The filtrate was washed with 600 ml of ethanol and dried at 60° C. in vacuo. A 290 gm quantity of the bis-imine with a melting point of 215°–220° C. (decomposition) was isolated (90% yield, based on the tetrasodium salt). IR (KBr) pellet: 1630 cm^{-1} (C=N), ^1H NMR (D_2O, 400 MHz) delta 8.88 (s, —N=CH), 7.54 (s, pyr-H), 4.70 (d, CH_2OP, J_{HP}=6.3 Hz), 4.06 (s, NC_2CH_2N), 2.21 (s, pyr-CH_3).

EXAMPLE 2

N,N'-bis(pyridoxal-5-phosphate)alkyldiimines

Repeating the procedure of Example 1 but replacing the 1,2-diaminoethane with 1,3-diamino-n-propane, 1,2-diamino-n-propane, 1,2-diaminoisopropane, 1,2-diamino-n-butane, 1,4-diamino-n-butane, 1,3-diamino-n-butane, 1,2-diamino-3-methylpropane yields the corresponding N,N'-bis(pyridoxal-5-phosphate)-1,3-(n-propylene)diimine, N,N'-bis(pyridoxal-5-phosphate)-1,2-(n-propylene)diimine, N,N'-bis(pyridoxal-5-phosphate)-1,2-isopropylenediimine, N,N'-bis(pyridoxal-5-phosphate)-1,2-(n-butylene)diimine, N,N'-bis(pyridoxal-5-phosphate)-1,4-(n-butylene)diimine, N,N'-bis(pyridoxal-5-phosphate)-1,3-(n-butylene)diimine, and N,N'-bis(pyridoxal-5-phosphate)-1,2-(3-methyl)propylenediimine.

EXAMPLE 3

N,N'-bis(pyridoxal-5-phosphate)ethylenediamine

The diimine from Example 1 was charged to a 5 liter 3-neck flask fitted with mechanical stirrer, fritted tube bubbler, and a 3-way stopcock. Then 1.5 liters of deionized water was added, followed by 1.5 liters of methanol. The yellow solution formed was stirred while sparging with nitrogen. Then 13 gm of 5% Pt on carbon (Aldrich Chem. Co.) was added, and the apparatus was purged with hydrogen. The reaction was allowed to proceed for 5 hr with continuous addition of hydrogen. HPLC analysis showed complete reduction to the amine. The reaction mixture was sparged with nitrogen for 15 min and then filtered through Celite. The filtrate was concentrated in vacuo at 60° C. to about 500 ml. The solution, containing N,N'-bis(pyridoxal-5-phosphate)ethylenediamine or 5-(N-(3-hydroxy-2-methyl-5-phosponomethyl-4-pyridyl)methylaminoethyleneaminomethyl)-2-hydroxy-3-methyl-5-pyridylmethylphosphoric acid salt was used directly for the next step. If desired the diamine can be isolated as off-white crystals by the addition of 200 ml of 97% formic acid and allowing the product to crystallize at room temperature overnight. The diamine is isolated by filtration and washed with 2×150 ml of cold deionized water. ^1H NMR (D_2O, 400 MHz) delta 7.47 (s, pyr-H), 4.58 (d, CH_2OP, J_{HP}=6.3 Hz), 3.94 (s, NCH_2CH_2N), 2.88 (s, N-CH_2-pyr), 2.16 (s, pyr-CH_3).

EXAMPLE 4

N,N'-bis(pyridoxal-5-phosphate)alkyldiamines

Repeating the procedure of Example 3 but substituting the diimine products of Example 2 for the diimine product of Example 1 yields N,N'-bis(pyridoxal-5-phosphate)-1,3-(n-propylene)diamine, N,N'-bis(pyridoxal-5-phosphate)-1,2-(n-propylene)diamine, N,N'-bis(pyridoxal-5-phosphate)-1,2-isopropylenediamine, N,N'-bis(pyridoxal-5-phosphate)-1,2-(n-butylene)diamine, N,N'-bis(pyridoxal-5-phosphate)-1,4-(n-butylene)diamine, N,N'-bis(pyridoxal-5-phosphate)-1,3-(n-butylene)diamine, and N,N'-bis(pyridoxal-5-phosphate)-1,2-(3-methyl)propylenediamine.

EXAMPLE 5

DPDP Synthesis

The diamine from Example 3 was charged to a two liter 4-neck flask equipped with two addition funnels, pH electrode, thermometer and stir bar. A 100 gm (2.5 mole) quantity of NaOH was dissolved in 200 ml of deionized water, and 130 gm (0.9 mole) of bromoacetic acid (Sigma Chem. Co.) was dissolved in 180 ml of deionized water. Each solution was charged to an addition funnel. Enough NaOH solution was added to the diamine solution to bring the pH to 11. The temperature of the reaction was raised to 42° C., and bromoacetic acid and NaOH solution were added concurrently to maintain the pH at 11. The addition was stopped at 45 min, and the progress of the reaction was checked by HPLC. The addition of bromoacetic acid and NaOH was resumed, and the reaction checked at 60 and 75 min. All the bromoacetic acid had been added, and the reaction was complete by HPLC analysis. Approximately 30 ml of the 50% NaOH solution remained in the addition funnel. A 675 gm quantity of cation exchange resin (AMBERLITE IRC-50) was added, and the mixture was placed in a refrigerator for 14 hr. The pH had dropped to 6.5. The resin was removed by filtration, and the filtrate treated with 260 gm of cation exchange resin (DOWEX 50W-X8). The pH dropped to about 4. The resin was removed by filtration, and the solution was concentrated in vacuo at 60° C. to a viscous oil. The oil was dried in vacuo for 48 hr at 25° C. to yield a resinous solid containing N,N'-bis-(pyridoxal-5-phosphate)ethylenediamine-N,N'-diacetic acid or N,N'-bis(3-hydroxy-2-methyl-5-phosphonomethyl-4-pyridylmethyl)ethylenediamine-N,N'-diacetic acid (DPDP).

EXAMPLE 6

DPDP Purification

The resinous solid obtained in Example 5 was dissolved in 600 ml of 88% formic acid, 1.5 liters of metha-

nol followed by 2.2 liters of ethanol was added, and the mixture was cooled to 0° C. for 2 hr. The solvent mixture was decanted from the resulting gum and discarded. The gum was dissolved in about 800 ml of deionized water which was then concentrated in vacuo to about 600–650 ml. Seed crystals were added, and the solution was allowed to stand at rm temp overnight. The product was isolated by filtration, washed with about 400 ml of cold deionized water, 250 ml of ethanol, and then dried in vacuo to yield 65 gm of DPDP in 85–90% purity by HPLC. The filtrate and washings were retained, concentrated in vacuo to about 350 ml, and the solution refrigerated until column chromatographic purification of the second crop.

The 65 gms of product was then dissolved in 75 ml of 88% formic acid containing 5 ml of deionized water with gentle heating to about 60° C. Cold deionized water was added to a total volume of one liter, and the solution was allowed to stand at 25° C. for 16 hr to crystallize. The product was isolated by filtration, washed with 200 ml cold deionized water, and dried in vacuo at 60° C. to yield 55 gms of DPDP in 93–95% purity by HPLC. A second recrystallization, using the same procedure yields 50 gm of DPDP in 96–98% purity by HPLC, mp 174°–180° C. with decomposition. Analysis: (Calculated for $C_{22}H_{32}N_4O_{14}P_2$) C, 41.38; H, 5.05; N, 8.77. (Found) C, 40.70; H, 5.14; N, 8.61. ^1H NMR (D_2O, 400 MHz) delta 7.93 (s, pyr-H), 4.81 (d, CH_2OP, J_{HP}=6.3 Hz), 4.07 (s, NCH_2CH_2N), 3.35 (s, CH_2COOH), 2.83 (s, N-CH_2-pyr), 2.38 (s, pyr-CH_3). ^{31}P NMR (D_2O, 161 MHz) delta -1.61 (s, CH_2OP, H_3PO_4 reference).

EXAMPLE 7

Sodium-Calcium Salt of Mn(DPDP)

A 4.16 gm (6.25 mmole) portion of DPDP from Example 6 was dissolved in 15 ml of rigorously degassed water by the addition of 1.0 gm (25 mmoles) of NaOH. A 1.25 gm (6.25 mmole) quantity of manganese dichloride tetrahydrate was added, and the solution immediately turned yellow. After stirring for 30 min, 0.25 gm (6.25 mmole) of solid NaOH was added to bring the pH up to 6.5. Then 0.15 gm (1.0 mmole) of calcium chloride was added, and sufficient degassed water was added to bring the volume of the solution to 25 ml. The clear yellow solution was sterilized by being filtered through a 0.2 micron filter to yield the sodium-calcium salt of a manganese chelate complex of N,N,-bis-(pyridoxal-5-phosphate)ethylenediamine-N,N'-diacetic acid or N,N'-bis(3-hydroxy-2-methyl-5-phosphonomethyl-4-pyridylmethyl)ethylenediamine-N,N'-diacetic acid.

EXAMPLE 8

Relaxivities with Mn(DPDP)

The relations of protons present in water and plasma exposed to the chelate product of Example 7 was tested by NMR for relaxities, in msec, at 10 MHz, 37° C. The results are shown in Table I.

TABLE I

	Relaxivities, msec.			
Molar Conc.	T_1 (Water)	T_2 (Water)	T_1 (Plasma)	T_2 (Plasma)
0.010	43	41	40	34
0.005	100	86	74	68
0.0025	175		139	124
0.00125	332		240	
0.000625	639		398	
0.000312	1083		624	
0.000156	1470		856	
0.000078			995	
0.000039			1103	

EXAMPLE 9

Organ Distribution of Mn(DPDP) in Rabbits

Each of four rabbits was injected intravenously with one of the following amounts of the solution obtained in Example 7: 0.01 mmoles/kg, 0.05 mmoles/kg, 0.10 mmoles/kg and 0.20 mmoles/kg. The rabbits were sacrificed 30 min post injection, and the proton relaxation values of selected body organs were measured with NMR, in vitro at 10 MHz. The relaxation rates found are shown in Table II.

TABLE II

			Relaxivities. msec. Observed Values Dose (mmol/kg)							
	Normal Values		0.01		0.05		0.10		0.20	
Tissue	T_1	T_2	T_1	T_2	T_1	T_2	T_1	T_2	T_1	T_2
Brain	—	—	554	76	496	82	590	90	352	66
Heart	605	70	—	—	353	54	300	51	205	47
Lung	595	112	—	—	575	113	435	61	376	63
Fat	171	154	—	—	200	139	183	115	192	—
Skel. Musc.	423	47	—	—	494	47	425	31	232	31
Renal Cort.	338	85	298	65	210	57	188	55	143	53
Renal Med.	672	149	502	99	223	57	209	48	127	60
Liver	252	64	176	39	76	31	65	23	68	25
Stom.	349	69	—	—	245	41	242	52	271	53
Small Int.	352	79	324	72	237	52	218	46	131	46
Large Int.	349	77	283	64	365	83	290	57	256	74
Urine	—	—	821	—	150	136	90	75	—	—
Blood	900	—	844	—	613	—	506	—	411	—

The organ distribution data is plotted in FIG. 2, with the following symbols:

Liver	-l-	Heart	-h-	Cortex	-c-
Medula	-m-	Urine	-u-	Blood	-b-

It shows rapid uptake of the Mn(DPDP) in the heart, liver and kidneys. The liver and kidneys are saturated with a dose of 0.10 mmole/kg while the heart continues to uptake Mn(DPDP) through the dose range studied. The complex of Mn(DPDP) may cross the intake-brain barrier as uptake by the brain was observed at higher doses. In cases where a defect is present in the blood-brain barrier (through disease or trauma), large amounts of the complex of Mn(DPDP) collect in the extravascular space and such defects were observed by NMRI tomography. The same defects are not observable without the use of Mn(DPDP) as a contrast agent.

EXAMPLE 10

Pharmacokinetics with Mn(DPDP)

Each of seven rabbits was injected intravenously with 0.01 mmol/kg of the solution obtained in Example 7. The rabbits were sacrificed at 0.25, 0.50, 1.0, 2.0, 4, 6 and 24 hours post-injection, and the proton relation values of selected body organs were measured with NMR, in vitro, at 10 MHz. The T_1 relaxation rates are shown in Table III.

TABLE III

	T_1 Relaxivities, msec							
	Time, hr							T_1 Normal
Tissue	0.25	0.50	1.0	2	4	6	24	Value
Liver	68	76	48	48	145	209	315	250 ± 50
Bile	160	46	25	21	<1	14	107	275 ± 55
Renal cortex	202	191	229	192	210	239	328	338 ± 60
Renal medulla	192	231	236	310	340	375	563	672 ± 100
Heart	231	352	381	507	522	663	660	605 ± 100

The pharmacokinetic data show rapid uptake and clearance of Mn(DPDP) in the liver, renal cortex, renal medulla and heart. The results indicate clearance of Mn(DPDP) through both the renal and hepatobiliary systems within 6–8 hours post-injection.

EXAMPLE 11

Potentiometric Titrations

The compound DPDP was studied potentiometrically from pH 11.2 to 2.0. Data sets were collected on a custom-built automatic potentiometric titration apparatus composed of a METROHM 655 DOSIMAT automatic buret, a FISHER ACCUMET pH meter with a CORNING calomel combination electrode, a custom-blown water jacketed titration cell, a BRINKMAN LAUDA K-2/R constant temperature bath and a COMMODORE 64 computer. The BASIC computer program TITRATOR (Harris, W. et al, *J. Am. Chem. Soc.* 101:6534 (1979)) runs the apparatus. Data analysis was performed on an IBM-AT computer using the least squares program, BETA (Harris, W. et al, supra), and the data analysis program, HANDNBAR (Harris, W. et al, supra). The titrants were standardized by phenophthalein titration as follows: KOH was calibrated against potassium hydrogen phthalate (a primary standard), and HCl solutions were calibrated against the KOH standard. The $Mn(II)Cl_2$ solution was standardized with an EDTA titration using Erichrome Black T as the indicator. All solutions were made from distilled, deionized water that was further purified on a MILLI-Q cartridge system, degassed, and then kept under an atmosphere of argon which had been scrubbed for CO_2 and O_2. Additions of EDTA and Mn(II) solutions were performed using calibrated GILMOT pipets. The electrode was calibrated in concentration units with degassed solutions of p[H+]=2.291 and 1.078 at 0.1M ionic strength.

The ligand proton titration was performed by adding 28.7 mg (0.045 mmoles) to 54.6 ml of a high pH aqueous solution. It was then titrated to low pH with 0.1009N HCl.

The metal complex titration was performed by adding 152.2 mg (0.2383 mmoles) to 74.6 ml of a high pH aqueous solution. 2.07 ml of a 0.1152M Mn(II) solution (0.2386 mmoles) were added. The complex was then titrated to low pH with 1.002N HCl.

The data obtained was analyzed using a model that consisted of eight one-proton steps. The first two protonation equilibria were outside of the range of the titration window afforded by the concentration of titrant and were therefore estimated based on work by Martell and co-workers reported by Taliaferro, C. et al, *Inorg. Chem.* 24:2408–2413 (1985). Refinement of the remaining equilibria yielded constants with calculated e.s.d.'s (log K) of less than 0.02. Assignment of the protonation sites (pK's) was based on work by Martell and co-workers (Taliaferro, et al, supra), and is shown in FIG. 1.

At a pH of 3 and above, the ligand is anionic and possesses deprotonated metal binding sites, both important criteria for a metal chelating agent.

EXAMPLE 12

N,N'-bis-(pyridoxal-5-phosphate)alkylenediamine-N,N'-diacetic acids

Repeating the procedure of Examples 5 and 6 but replacing the diamine of Example 3 with the products of Example 4 yields

N,N'-bis(pyridoxal-5-phosphate)-1,3-(n-propylene)-N,N'-diacetic acid,

N,N'-bis(pyridoxal-5-phosphate)-1,2-(n-propylene)-N,N'-diacetic acid,

N,N'-bis(pyridoxal-5-phosphate)-1,2-isopropylene-N,N'-diacetic acid,

N,N'-bis(pyridoxal-5-phosphate)-1,2-(n-butylene)-N,N'-diacetic acid,

N,N'-bis(pyridoxal-5-phosphate)-1,4-(n-butylene)-N,N'-diacetic acid,

N,N'-bis(pyridoxal-5-phosphate)-1,3-(n-butylene)-N,N'-diacetic acid, and

N,N'-bis(pyridoxal-5-phosphate)-1,2-(3-methylene)propyl-N,N'-diacetic acid.

EXAMPLE 13

DPDP Chelates

Repeating the procedure of Example 7 but replacing manganese dichloride tetrahydrate with equimolar amounts of the soluble chlorides of Cr^{+3}, Fe^{+2}, Fe^{+3}, Co^{+3}, Ni^{+2}, Cu^{+2}, Pr^{+3}, Nd^{+3}, Sm^{+3}, Yb^{+3}, Gd^{+3},

Tb^{+3}, Ho^{+3}, or Er^{+3} yields the corresponding sodium salts of the respective metal ion chelates of N,N'-bis-(pyridoxal-5-phosphate)ethylenediamine-N,N'-diacetic acid. The procedure can be repeated replacing the metal chloride salts with soluble nitrate or sulfate salts.

EXAMPLE 14

Other Chelates

Repeating the procedure of Example 7 but replacing N,N'-bis-(pyridoxal-5-phosphate)ethylenediamine-N,N'-diacetic acid with equimolar amounts of the chelate forming compounds produced in accordance with Example 10, and replacing manganese dichloride tetrahydrate with equimolar amounts of the soluble chlorides, carbonates or nitrates of Cr^{+3}, Fe^{+2}, Fe^{+3}, Co^{+3}, Ni^{+2}, Cu^{+2}, Pr^{+3}, Nd^{+3}, Sm^{+3}, Yb^{+3}, Gd^{+3}, Tb^{+3}, Ho^{+3}, or Er^{+3} yields the sodium-calcium salts of the respective metal ion chelates of

N,N'-bis(pyridoxal-5-phosphate)-1,3-(n-propylene)-N,N'-diacetic acid,

N,N'-bis(pyridoxal-5-phosphate)-1,2-(n-propylene)-N,N'-diacetic acid,

N,n'-bis(pyridoxal-5-phosphate)-1,2-isopropylene-N,N'-diacetic acid,

N,N'-bis(pyridoxal-5-phosphate)-1,2-(n-butylene)-N,N'-diacetic acid,

N,N'-bis(pyridoxal-5-phosphate)-1,4-(n-butylene)-N,N'-diacetic acid,

N,N'-bis(pyridoxal-5-phosphate)-1,3-(n-butylene)-N,N'-diacetic acid, and

N,N'-bis(pyridoxal-5-phosphate)-1,2-(3-methylene)propyl-N,N'diacetic acid.

EXAMPLE 15

N,N'-bis(pyridoxal-5-phosphate)trans-1,2-cyclohexylenediimine

A 26.5 gm quantity (0.1 mole) of pyridoxal-5-phosphate was dissolved in 300 ml of methanol, and 38 ml of 5N NaOH was added. Then 5.71 gm (0.05 mole) of trans-1,2-diaminocyclohexane was added with stirring, and the volume of the solution was reduced to 200 ml in vacuo. After cooling to 0° C., the yellow imine was isolated by filtration, washed with diethyl ether, and dried in vacuo to yield 17 gm of sodium N,N'-bis(pyridoxal-5-phosphate)-trans-1,2-cyclohexylenediimine or sodium 5-(N-(3-hydroxy-2-methyl-5-phosphonomethyl-4-pyridyl)methylideneamino-trans-1,2-cyclohexyleneiminomethyl)-2-hydroxy-3-methyl-5-pyridylmethylphosphate (49% yield, melting point 200°–205° C. with decomposition).

EXAMPLE 16

Other N,N'-bis(pyridoxal-5-phosphate)-1,2-cyclo(alkylene or arylene)diimines

Repeating the procedure of Example 15 but replacing the trans-1,2-diaminocyclohexane with trans-1,2-diaminocyclopentane, trans-1,2-diaminocycloheptane, trans-1,2-diaminocyclooctane, cis-1,2-diaminocyclohexane, trans-1,3-diaminocyclohexane, trans-1,4-diaminocyclohexane, o-aminoaniline and cis-1,4-diaminocyclohexane yields the corresponding

N,N'-bis(pyridoxal-5-phosphate)-trans-1,2-cyclopentylenediimine,

N,N'-bis(pyridoxal-5-phosphate)-trans-1,2-cycloheptylenediimine,

N,N'-bis(pyridoxal-5-phosphate)-trans-1,2-cyclooctylenediimine,

N,N'-bis(pyridoxal-5-phosphate)-cis-1,2-cyclohexylenediimine,

N,N'-bis(pyridoxal-5-phosphate)-trans-1,3-cyclohexylenediimine,

N,N'-bis(pyridoxal-5-phosphate)-trans-1,4-cyclohexylenediimine,

N,N'-bis(pyridoxal-5-phosphate)-1,2-phenylenediimine, and

N,N'-bis(pyridoxal-5-phosphate)-cis-1,4-cyclohexylenediimine.

EXAMPLE 17

N,N'-bis(pyridoxal-5-phosphate)trans-1,2-cyclohexylenediamine

A 14 gm (0.02 mole) portion of the diimine product of Example 15 was dissolved in 200 ml of 1:1 water:methanol. The resulting solution was sparged with argon, and 1.0 gm of 5% platinum on carbon was added. The system was flushed with hydrogen. The hydrogen pressure was increased to 50 psig for 16 hr at 25° C. The reaction product was filtered through CELITE, and the resulting solution of N,N'-bis(pyridoxal-5-phosphate)-trans-1,2-cyclohexyldiamine or sodium 5-(N-(3-hydroxy-2-methyl-5-phosphonomethyl-4-pyridyl)methylideneamino-trans-1,2-cyclohexyliminomethyl)-2-hydroxy-3-methyl-5-pyridylmethylphosphate was concentrated in vacuo to about 20 ml and cooled to 0° C. to induce crystallization. The product was isolated by filtration, washed with cold H_2O and dried in vacuo. ^1H NMR (D_2O, 400 MHz) delta 7.45 (s, pyr-H), 4.53 (d, CH_2OP, J_{HP}=4.9 Hz), 3.83 (dd, N-CH_2-pyr), 2.72 (br s, cyclo-$(CH_2)_4(CH)_2(NH)_2$-), 1.88 (s, pyr-CH_3), 1.83–1.08 (3 br s, cyclo-$(CH_2)_4(CH)_2(NH)_2$-).

EXAMPLE 18

N,N'-bis(pyridoxal-5-phosphate)-1,2-cyclo(alkylene or arylene)diamines

Repeating the procedure of Example 17 but replacing the diimine product of Example 15 with the diimine products prepared in accordance with the procedure of Example 16 yields the corresponding diamines:

N,N'-bis(pyridoxal-5-phosphate)-trans-1,2-cyclopentylenediamine,

N,N'-bis(pyridoxal-5-phosphate)-trans-1,2-cycloheptylenediamine,

N,N'-bis(pyridoxal-5-phosphate)-trans-1,2-cyclooctylenediamine,

N,n'-bis(pyridoxal-5-phosphate)-cis-1,2-cyclohexylenediamine,

N,N'-bis(pyridoxal-5-phosphate)-trans-1,3-cyclohexylenediamine,

N,N'-bis(pyridoxal-5-phosphate)-trans-1,4-cyclohexylenediamine,

N,N'-bis(pyridoxal-5-phosphate)-1,2-phenylenediamine, and

N,N'-bis(pyridoxal-5-phosphate)-cis-1,4-cyclohexylenediamine.

EXAMPLE 19

N,N'-bis-(pyridoxal-5-phosphate)-trans-1,2-cyclohexylenediamine-N,N'-diacetic acid

The diamine from Example 17 was charged to a one liter 3-neck flask, and the pH was adjusted to 11 with 5N NaOH. Then 5.6 gm (0.04 mole) of bromoacetic

acid was dissolved in 10 ml of water and added dropwise to the stirred diamine solution while maintaining the pH at 11. The reaction was warmed to 50° C. and stirred for 16 hr. 50 gm of weakly acidic cation exchange resin (AMBERLITE IRC-50) was added, and the pH dropped to 6.7. The resin was removed by filtration, and 15 gm of cation exchange resin (DOWEX 50W-X8) was added. The pH dropped to 3.8.

The solution was filtered, and all of the solvent was evaporated from the filtrate to yield a foamy solid. The solid was dissolved in 30 ml of 88% formic acid, and the product was precipitated by the addition of 150 ml of methanol followed by 150 ml of ethanol. The solvent mixture was decanted from the gummy solid and discarded. The solid was dissolved in a minimum amount of deionized water (about 100 ml), and the product was allowed to stand overnight at 25° C. The product was isolated by filtration, washed with 50 ml of cold water, 25 ml of ethanol and then dried in vacuo to yield the product. The compound was recrystallized by the same procedure to yield N,N'-bis-(pyridoxal-5-phosphate)-trans-1,2-cyclohexylenediamine-N,N'-diacetic acid or N,N'-bis(3-hydroxy-2-methyl-5-phosphonomethyl-4-pyridylmethyl)-trans-1,2-cyclohexylenediamine-N,N'-diacetic acid (DPCP) with a melting point (decomposition) of 221°–226° C. ^1H NMR (D_2O, 400 MHz) delta 7.53 (s, pyr-H), 4.58 (d, CH_2OP, J_{HP}=5.9 Hz), 3.89 (dd, N-CH_2-pyr), 3.31 (s, CH_2COOH), 2.78 (br s, cyclo-$(CH_2)_4(CH)_2(NH)_2$-), 1.93 (s, pyr-CH_3), 1.90–1.15 (3 br s, cyclo-$(CH_2)_4(CH)_2(NH)_2$-).

EXAMPLE 20

N,N'-bis-(pyridoxal-5-phosphate)cyclo(alkylene and arylene)diamine-N,N'-diacetic acids

Repeating the procedure of Example 19 but replacing the diamine of Example 17 with the diamines of Example 18 yields the corresponding:

N,N'-bis(pyridoxal-5-phosphate)-trans-1,2-cyclopentylenediamine-N,N'-diacetic acid,
N,N'-bis(pyridoxal-5-phosphate)-trans-1,2-cycloheptylenediamine-N,N'-diacetic acid,
N,N'-bis(pyridoxal-5-phosphate)-trans-1,2-cyclooctylenediamine-N,N'-diacetic acid,
N,N'-bis(pyridoxal-5-phosphate)-cis-1,2-cyclohexylenediamine-N,N'-diacetic acid,
N,N'-bis(pyridoxal-5-phosphate)-trans-1,3-cyclohexylenediamine-N,N'-diacetic acid,
N,N'-bis(pyridoxal-5-phosphate)-trans-1,4-cyclohexylenediamine-N,N'-diacetic acid,
N,N'-bis(pyridoxal-5-phosphate)-1,2-phenylenediamine-N,N'-diacetic acid, and
N,N'-bis(pyridoxal-5-phosphate)-cis-1,4-cyclohexylenediamine-N,N'-diacetic acid.

EXAMPLE 21

Chelates

Repeating the procedure of Example 7 but replacing N,N'-bis-(pyridoxal-5-phosphate)ethylenediamine-N,N'-diacetic acid with equimolar amounts of the products of chelate forming compounds produced in accordance with Examples 19 and 20 and using equimolar amounts of the soluble chlorides, carbonates or nitrates of Mn^{+2}, Cr^{+3}, Fe^{+2}, Fe^{+3}, Co^{+3}, Ni^{+2}, Cu^{+2}, Pr^{+3}, Nd^{+3}, Sm^{+3}, Yb^{+3}, Gd^{+3}, Tb^{+3}, Ho^{+3}, or Er^{+3} yields the sodium-calcium salts of the respective metal ion chelates of

N,N'-bis(pyridoxal-5-phosphate)-trans-1,2-cyclohexylenediamine-N,N'-diacetic acid,
N,N'-bis(pyridoxal-5-phosphate)-trans-1,2-cyclopentylenediamine-N,N'-diacetic acid,
N,N'-bis(pyridoxal-5-phosphate)-trans-1,2-cycloheptylenediamine-N,N'-diacetic acid,
N,N'-bis(pyridoxal-5-phosphate)-trans-1,2-cyclooctylenediamine-N,N'-diacetic acid,
N,N'-bis(pyridoxal-5-phosphate)-cis-1,2-cyclohexylenediamine-N,N'-diacetic acid,
N,N'-bis(pyridoxal-5-phosphate)-trans-1,3-cyclohexylenediamine-N,N'-diacetic acid,
N,N'-bis(pyridoxal-5-phosphate)-trans-1,4-cyclohexylenediamine-N,N'-diacetic acid,
N,N'-bis(pyridoxal-5-phosphate)-1,2-phenylenediamine-N,N'-diacetic acid, and
N,N'-bis(pyridoxal-5-phosphate)-cis-1,4-cyclohexylenediamine-N,N'-diacetic acid.

EXAMPLE 22

Pyridoxal-5-phosphate (N-methylethanolamine)monoester

2.04 gm (0.01 mole) of pyridoxal hydrochloride is dissolved in 50 ml of dry THF containing 0.05 gm (0.02 mole) of sodium hydride with stirring. When gas evolution had ceased (about 15 min), 1.71 gm (0.01 mole) of benzyl bromide is added, and after stirring overnight, the solution is brought to dryness in vacuo. The sticky solid is suspended in 50 ml of dry methylene chloride and following addition of 3.0 gm (0.03 mole) of triethylamine, the slurry is cooled to 0° C. 1.38 gm (0.01 mole) of 2-chloro-3-methyl-1-oxa-3-aza-2-phosphacyclopentane (prepared by the method of Jones, et al, *J. Chem. Soc.* Perkin trans I. p 199 (1985)) is added with vigorous stirring. The suspension is stirred for 1 hr at rm temp, and then 100 ml of water is added. The methylene chloride layer is separated, dried over $MgSO_4$, and the solvent removed in vacuo. Addition of diethyl ether yields the intermediate product as a hydroscopic white solid (1.8 gm, 50% yield). The intermediate is oxidized with excess dinitrogen tetroxide in methylene chloride at −78° C., and then is treated with aqueous HCl in THF under reflux to give the (N-methylethanolamine)monoester of pyridoxal-5-phosphate in an overall yield of 40%.

EXAMPLE 23

N,N'-bis(pyridoxal-5-phosphate(N-methylethanolamine)monoester)ethylenediimine

Repeating the procedure of Example 1 but replacing pyridoxal-5-phosphate with the product of Example 22 yields N,N'-bis(pyridoxal-5-phosphate(N-methylethanolamine)monoester)ethylenediimine or sodium 5-(N-(3-hydroxy-2-methyl-5-phosponomethyl-4-pyridyl)-methylideneaminoethyleneiminomethyl)-2-hydroxy-3-methyl-5-pyridylmethylphosphoric acid, N-methylethanolamine ester.

EXAMPLE 24

Other Monoester Diimines

Repeating the procedure of Example 23 with 1,3-diamino-n-propane, 1,2-diamino-n-propane, 1,2-diaminoisopropane, 1,2-diamino-n-butane, 1,4-diamino-n-butane, 1,3-diamino-n-butane, and 1,2-diamino-3-methylpropane yields the corresponding N,N'-bis(pyridoxal-5-phosphate(N-methylethanolamine)monoester)-

1,3-(n-propylene)diimine, N,N'-bis(pyridoxal-5-phosphate(N-methylethanolamine)monoester)-1,2-(n-propylene)diimine, N,N'-bis(pyridoxal-5-phosphate(N-methylethanolamine)monoester)-1,2-isopropylenediimine, N,N'-bis(pyridoxal-5-phosphate(N-methylethanolamine)monoester)-1,2-(n-butylene)diimine, N,N'-bis(pyridoxal-5-phosphate(N-methylethanolamine)-monoester)-1,4-(n-butylene)diimine, N,N'-bis(pyridoxal-5-phosphate(N-methylethanolamine)monoester)-1,3-(n-butylene)diimine, and N,N'-bis(pyridoxal-5-phosphate(N-methylethanolamine)monoester)-1,2-(3-methyl)propylenediimine.

Repeating the procedure of Example 23 with trans-1,2-diaminocyclohexane, trans-1,2-diaminocyclopentane, trans-1,2-diaminocycloheptane, trans-1,2-diaminocyclooctane, o-aminoaniline, and cis-1,2-diaminocyclohexane, yields the corresponding N,N'-bis(pyridoxal-5-phosphate(N-methylethanolamine)-monoester)-trans-1,2-cyclohexylenediimine,

N,N'-bis(pyridoxal-5-phosphate(N-methylethanolamine)monoester)-trans-1,2-cyclopentylenediimine,

N,N'-bis(pyridoxal-5-phosphate(N-methylethanolamine)monoester)-trans-1,2-cycloheptylenediimine,

N,N'-bis(pyridoxal-5-phosphate(N-methylethanolamine)monoester)-trans-1,2-cyclooctylenediimine,

N,N'-bis(pyridoxal-5-phosphate(N-methylethanolamine)monoester)-1,2-phenylenediimine, and

N,N'-bis(pyridoxal-5-phosphate(N-methylethanolamine)monoester)-cis-1,2-cyclohexylenediimine.

EXAMPLE 25

N,N'-bis(pyridoxal-5-phosphate(N-methylethanolamine)monoester)ethylenediamine

Repeating the procedure of Example 3 but substituting the diimine product of Example 23 for the diimine product of Example 1 yields N,N'-bis(pyridoxal-5-phosphate(N-methyl-ethanolamine)monoester)ethylenediamine or 5-(N-(3-hydroxy-2-methyl-5-phosponomethyl-4-pyridyl)methylaminoethyleneaminomethyl)-2-hydroxy-3-methyl-5-pyridylmethylphosphoric acid, N-methyl-ethanolamine ester.

EXAMPLE 26

Other Monoester Diamines

Repeating the procedure of Example 25 but substituting the diimine products of Example 24 for the diimine product of Example 23 yields

N,N'-bis(pyridoxal-5-phosphate(N-methylethanolamine)monoester)-1,3-(n-propylene)diamine,

N,N'-bis(pyridoxal-5-phosphate(N-methylethanolamine)monoester)-1,2-(n-propylene)diamine,

N,N'-bis(pyridoxal-5-phosphate(N-methylethanolamine)monoester)-1,2-isopropylenediamine,

N,N'-bis(pyridoxal-5-phosphate(N-methylethanolamine)monoester)-1,2-(n-butylene)diamine,

N,N'-bis(pyridoxal-5-phosphate(N-methylethanolamine)monoester)-1,4-(n-butylene)diamine,

N,N'-bis(pyridoxal-5-phosphate(N-methylethanolamine)monoester)-1,3-(n-butylene)diamine,

N,N'-bis(pyridoxal-5-phosphate(N-methylethanolamine)monoester)-1,2-(3-methyl)propylenediamine,

N,N'-bis(pyridoxal-5-phosphate(N-methylethanolamine)monoester)-trans-1,2-cyclohexylenediamine,

N,N'-bis(pyridoxal-5-phosphate(N-methylethanolamine)monoester)-trans-1,2-cyclopentylenediamine,

N,N'-bis(pyridoxal-5-phosphate(N-methylethanolamine)monoester)-trans-1,2-cycloheptylenediamine,

N,N'-bis(pyridoxal-5-phosphate(N-methylethanolamine)monoester)-trans-1,2-cyclooctylenediamine,

N,N'-bis(pyridoxal-5-phosphate(N-methylethanolamine)monoester)-1,2-phenylenediamine, and

N,N'-bis(pyridoxal-5-phosphate(N-methylethanolamine)monoester)-cis-1,2-cyclohexylenediamine.

EXAMPLE 27

DPDP-phosphate monoester

Repeating the procedure of Examples 5 and 6 but replacing the diamine of Example 3 with the product of Example 25 yields N,N'-bis(pyridoxal-5-phosphate-(N-methyl-ethanolamine)monoester)ethylenediamine-N,N'-diacetic acid, sodium salt or N-methylethanolamine phosphate ester of 5-(N-(3-hydroxy-2-methyl-5-phosponomethyl-4-pyridyl)methylaminoethyleneaminomethyl)-2-hydroxy-3-methyl-5-pyridylmethylphosphoric acid, sodium salt.

EXAMPLE 28

Other Diamine-N,N'-diacetic Acid Phosphate Monoesters

Repeating the procedure of Example 27 but replacing the products of Example 26 for the product of Example 25 yields

N,N'-bis(pyridoxal-5-phosphate(N-methylethanolamine)monoester)-1,3-(n-propylene)diamine-N,N'-diacetic acid salt,

N,N'-bis(pyridoxal-5-phosphate(N-methylethanolamine)mono-ester)-1,2-(n-propylene)diamine-N,N'-diacetic acid salt,

N,N'-bis(pyridoxal-5-phosphate(N-methylethanolamine)monoester)-1,2-isopropylenediamine-N,N'-diacetic acid salt,

N,N'-bis(pyridoxal-5-phosphate(N-methylethanolamine)monoester)-1,2-(n-butylene)diamine-N,N'-diacetic acid salt,

N,N'-bis(pyridoxal-5-phosphate(N-methylethanolamine)monoester)-1,4-(n-butylene)diamine-N,N'-diacetic acid salt,

N,N'-bis(pyridoxal-5-phosphate(N-methylethanolamine)monoester)-1,3-(n-butylene)diamine-N,N'-diacetic acid salt,

N,N'-bis(pyridoxal-5-phosphate(N-methylethanolamine)monoester)-1,2-(3-methyl)propylenediamine-N,N'-diacetic acid salt,

N,N'-bis(pyridoxal-5-phosphate(N-methylethanolamine)monoester)-trans-1,2-cyclohexylenediamine-N,N'-diacetic acid salt,

N,N'-bis(pyridoxal-5-phosphate(N-methylethanolamine)monoester)-trans-1,2-cyclopentylenediamine-N,N'-diacetic acid salt,

N,N'-bis(pyridoxal-5-phosphate(N-methylethanolamine)monoester)-trans-1,2-cycloheptylenediamine-N,N'-diacetic acid salt,

N,N'-bis(pyridoxal-5-phosphate(N-methylethanolamine)monoester)-trans-1,2-cyclooctylenediamine-N,N'-diacetic acid salt,
N,N'-bis(pyridoxal-5-phosphate(N-methylethanolamine)monoester)-1,2-phenylenediamine-N,N'-diacetic acid salt, and
N,N'-bis(pyridoxal-5-phosphate(N-methylethanolamine)monoester)-cis-1,2-cyclohexylenediamine-N,N'-diacetic acid salt.

EXAMPLE 29

Chelates

Repeating the procedure of Example 7 but replacing N,N'-bis-(pyridoxal-5-phosphate)ethylenediamine-N,N'-diacetic acid with an equimolar amount of the chelate forming compound produced in accordance with Example 27, yields the sodium-calcium Mn(II) chelate of N,N'-bis(pyridoxal-5-phosphate-(N-methylethanolamine)monoester)ethylenediamine-N,N'-diacetic acid.

Repeating this procedure, replacing manganese dichloride tetrahydrate with equimolar amounts of the soluble chlorides, carbonates or nitrates of Cr^{+3}, Fe^{+2}, Fe^{+3}, Co^{+3}, Ni^{+2}, Cu^{+2}, Pr^{+3}, Nd^{+3}, Sm^{+3}, Yb^{+3}, Gd^{+3}, Tb^{+3}, Dy^{+3}, Ho^{+3}, or Er^{+3} yields the sodium-calcium salts of the respective metal ion chelates of N,N'-bis(pyridoxal-5-phosphate-(N-methylethanolamine)monoester)ethylenediamine-N,N'-diacetic acid.

EXAMPLE 30

Other Chelates

Repeating the procedures of Example 29 but replacing the products of Example 28 for the product of Example 27 yields the Mn^{+2}, Cr^{+3}, Fe^{+2}, Fe^{+3}, Co^{+3}, Ni^{+2}, Cu^{+2}, Pr^{+3}, Nd^{+3}, Sm^{+3}, Yb^{+3}, Gd^{+3}, Tb^{+3}, Ho^{+3}, or Er^{+3} ion chelates of the sodium-calcium salts of the diacetic acid chelating agents of Example 28.

EXAMPLE 31

DPDP-(mono)acetic Acid Analog Synthesis

10 gms (0.017 mole) of the diamine from Example 3 was dissolved in 25 ml of 1:1 water/methanol and charged to a 250 ml 4-neck flask equipped with two addition funnels, pH electrode, thermometer and stir bar. 1.4 gms (0.035 mole) of NaOH and 2.4 gm (0.017 mole) of bromoacetic acid were each dissolved in 10 ml of deionized water and charged to the two addition funnels. Sufficient NaOH was added to the stirring diamine solution to bring the pH to about 11, which raised the temperature to about 40° C. The temperature was maintained at 40° C., and bromoacetic acid and NaOH were added concurrently to maintain the pH at 11 over the course of 3 hr. The reaction was monitored by HPLC. Dowex 50W-X8 resin was added to lower the pH from 11.1 to 3.1, the solution was filtered, and resin was washed with 100 ml of deionized water. The pH of the filtrate was about 3.3. 5 ml of 97% formic acid was added, and the pH dropped to 3.0. Then 10 ml of isopropyl alcohol was added with a few seed crystals, the product stirred overnight at 30° to 40° C., and then allowed to cool to 25° C. The crude product was collected by filtration and washed with deionized water. The crude product was then dried at 50° C. in vacuo to yield 3 gms of product (30% yield). The product can be recrystallized from a formic acid/water mixture to yield 2.4 gms in 96–98% purity by HPLC to yield N,N'-bis-(pyridoxal-5-phosphate)ethylenediamine-N-acetic acid.

EXAMPLE 32

Other (Mono)acetic Acids

Repeating the procedure of Example 31 with the products of Examples 4, 17 and 18 yields the corresponding
N,N'-bis(pyridoxal-5-phosphate)-1,3-(n-propylene)diamine-N-acetic acid,
N,N'-bis(pyridoxal-5-phosphate)-1,2-(n-propylene)diamine-N-acetic acid,
N,N'-bis(pyridoxal-5-phosphate)-1,2-isopropylenediamine-N-acetic acid,
N,N'-bis(pyridoxal-5-phosphate)-1,2-(n-butylene)diamine-N-acetic acid,
N,N'-bis(pyridoxal-5-phosphate)-1,4-(n-butylene)diamine-N-acetic acid,
N,N'-bis(pyridoxal-5-phosphate)-1,3-(n-butylene)diamine-N-acetic acid,
N,N'-bis(pyridoxal-5-phosphate)-1,2-(3-methyl)-propylenediamine-N-acetic acid,
N,N'-bis(pyridoxal-5-phosphate)-trans-1,2-cyclohexylenediamine-N-acetic acid,
N,N'-bis(pyridoxal-5-phosphate)-trans-1,2-cyclopentylenediamine-N-acetic acid,
N,N'-bis(pyridoxal-5-phosphate)-trans-1,2-cycloheptylenediamine-N-acetic acid,
N,N'-bis(pyridoxal-5-phosphate)-trans-1,2-cyclooctylenediamine-N-acetic acid,
N,N'-bis(pyridoxal-5-phosphate)-cis-1,2-cyclohexylenediamine-N-acetic acid,
N,N'-bis(pyridoxal-5-phosphate)-trans-1,3-cylohexylenediamine-N-acetic acid,
N,N'-bis(pyridoxal-5-phosphate)-trans-1,4-cyclohexylenediamine-N-acetic acid,
N,N'-bis(pyridoxal-5-phosphate)-1,2-phenylenediamine-N-acetic acid, and
N,N'-bis(pyridoxal-5-phosphate)-cis-1,4-cyclohexylenediamine-N-acetic acid.

EXAMPLE 33

Other Chelates

Repeating the procedures of Example 29 but replacing the products of Example 32 for the product of Example 27 yields the Mn^{+2}, Cr^{+3}, Fe^{+2}, Fe^{+3}, Co^{+3}, Ni^{+2}, Cu^{+2}, Pr^{+3}, Nd^{+3}, Sm^{+3}, Yb^{+3}, Gd^{+3}, Tb^{+3}, Ho^{+3}, or Er^{+3} ion chelates of the sodium-calcium salts of the monoacetic acid chelating agents of Example 32.

EXAMPLE 34

N-pyridoxal-N'-(pyridoxal-5-phosphate)ethylenediimine

A 25 gm (0.123 mole) quantity of pyridoxal hydrochloride is slurried in 100 ml of methanol, and 4.88 gm (0.123 mole) of NaOH is added. When the solution is homogeneous, it is added dropwise to 7.5 gm of 1,2-diaminoethane in 100 ml of methanol with stirring. After 60 min, a methanol solution containing 32.7 gm (0.123 mole) of pyridoxal-5-phosphate and 4.88 gm (0.123 mole) of NaOH is added with vigorous stirring. The unsymmetrical imine product, 5-(N-(3-hydroxy-5-hydroxymethyl-2-methyl-4-pyridyl)methylideneaminoethyleneiminomethyl)-2-hydroxy-3-methyl-5-pyridylmethylphosphoric acid or N-pyridoxal-N'-(pyridoxal-5-phosphate)-ethylenediimine, is stirred for 1 hr, and the

product is isolated by filtration. The diimine is washed with methanol (2×50 ml) and diethyl ether (2×50 ml), and dried in vacuo.

EXAMPLE 35

N-pyridoxal-N'-(pyridoxal-5-phosphate)ethylenediamine

Repeating the procedure of Example 3 but substituting the diimine product of Example 34 for the diimine product of Example 1 yields the corresponding diamine product, 5-(N-(3-hydroxy-5-hydroxymethyl-2-methyl-4-pyridyl)methylaminoethyleneaminomethyl)-2-hydroxy-3-methyl-5-pyridylmethylphosphoric acid or N-pyridoxal-N'-(pyridoxal-5-phosphate)-ethylenediamine.

EXAMPLE 36

DPMP Synthesis

Repeating the procedures of Example 5 and 6 with the product of Example 35 yields the corresponding N-pyridoxal-N'-(pyridoxal-5-phosphate)ethylenediamine-N,N'-diacetic acid or N-(3-hydroxy-5-hydroxyomethyl-2-methyl-4-pyridylmethyl)-N'-(3-hydroxy-2-methyl-5-phosphonomethyl-4-pyridylmethyl)ethylenediamine-N,N'-diacetic acid (DPMP).

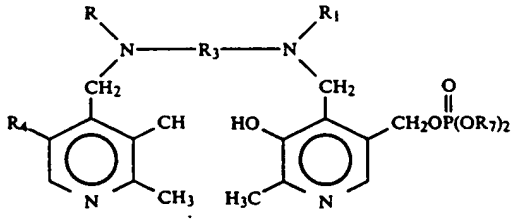
EXAMPLE 37

Other Chelates

Repeating the procedures of Example 29 but replacing the product of Example 36 for the product of Example 27 yields the Mn^{+2}, Cr^{+3}, Fe^{+2}, Fe^{+3}, Co^{+3}, Ni^{+2}, Cu^{+2}, Pr^{+3}, Nd^{+3}, Sm^{+3}, Yb^{+3}, Gd^{+3}, Tb^{+3}, Ho^{+3}, or Er^{+3} ion chelates of the sodium-calcium salts of N-pyridoxal-N'-(pyridoxal-5-phosphate)ethylenediamine-N,N'-diacetic acid.

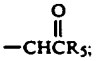
We claim:

1. A metal ion chelate of a chelating compound of the formula:

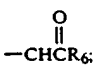

(I)

wherein:

R is hydrogen or



R_1 is hydrogen or



with the proviso that at least one of R and R_1 is other than hydrogen;

R_5 and R_6 are each, independently, hydroxy, alkoxy having from 1 to 18 carbons, hydroxy-substituted alkoxy having from 1 to 18 carbons, amino, or alkylamido having from 1 to 10 carbons;

R_3 is alkylene having from 1 to 8 carbons, 1,2-cycloalkylene having from 5 to 8 carbons, or 1,2-arylene having from 6 to 10 carbons;

R_4 is hydrogen, hydroxymethyl, alkyl having from 1 to 6 carbons, or

each R_7 is, independently, hydrogen, hydroxy-substituted alkyl having from 1 to 18 carbons, or aminoalkyl having from 1 to 18 carbons; and

the chelated metal ion is a paramagnetic ion of a metal having an atomic number of from 21 to 29, inclusive, 42, 44, or from 58 to 70, inclusive,

or a physiologically biocompatible inorganic or organic salt of said metal ion chelate.

2. A metal ion chelate according to claim 1 wherein R and R_1 are each other than hydrogen, or a salt of said metal ion chelate.

3. A metal ion chelate according to claim 1 wherein each R_7 is hydrogen, or a salt of said metal ion chelate.

4. A metal ion chelate according to claim 1 wherein R and R_1 are each other than hydrogen, R_5 and R_6 are each, independently, hydroxy, alkoxy having from 1 to 8 carbons, hydroxyethyl, dihydroxypropyl, amino, or alkylamido having from 1 to 8 carbons, or a salt of said metal ion chelate.

5. A metal ion chelate according to claim 4 wherein R_3 is alkylene having from 2 to 6 carbons, or a salt of said metal ion chelate.

6. A metal ion chelate of N,N'-bis(pyridoxal-5-phosphate)ethylenediamine-N,N'-diacetic acid or a salt thereof, wherein the metal ion is as recited in claim 1, or a salt of said metal ion chelate.

7. A metal ion chelate according to claim 4 wherein R_3 is cyclohexyl, or a salt of said metal ion chelate.

8. A metal ion chelate of N,N'-bis(pyridoxal-5-phosphate)-trans-1,2-cyclohexyldiamine-N,N'-diacetic acid or a salt thereof, wherein the metal ion is as recited in claim 1, or a salt of said metal ion chelate.

9. A metal ion chelate according to claim 1 wherein the metal ion is divalent or trivalent, or a salt of said metal ion chelate.

10. A metal ion chelate according to claim 1 wherein the metal ion is chromium (III), manganese (II), iron (III), iron (II), cobalt (II), nickel (II), copper (II), praseodymium (III), neodymium (III), samarium (III), ytterbium (III), gadolinium (III), terbium (III), dysprosium (III), holmium (III), or erbium (III), or a salt of said metal ion chelate.

11. A metal ion chelate according to claim 1 wherein the metal ion is manganese (II), or a salt of said metal ion chelate.

12. A manganese (II) chelate of N,N'-bis(pyridoxal-5-phosphate)ethylenediamine-N,N'-diacetic acid or a salt thereof, or a salt of said manganese (II) chelate.

13. A manganese (II) chelate of N,N'-bis(pyridoxal-5-phosphate)-trans-1,2-cyclohexyldiamine-N,N'-diacetic acid or a salt thereof, or a salt of said manganese (II) chelate.

14. A metal ion chelate according to claim 1 in the form of a calcium salt of an anionic chelate complex of a paramagnetic metal ion and a chelating compound of formula I, or a salt of said metal ion chelate.

15. A metal ion chelate or salt according to claim 14 wherein the molar ratio of calcium to chelating compound is from 0.05 to 1.0.

16. A metal ion chelate in the form of a calcium salt of the manganese (II) chelate of claim 12 or a salt thereof.

17. A metal ion chelate or salt according to claim 16 wherein the molar ratio of calcium to chelating compound is from 0.05 to 1.0.

18. A sodium-calcium salt of a manganese (II) chelate of N,N'-bis(pyridoxal-5-phosphate)ethylenediamine-N,N'-diacetic acid or a salt thereof.

* * * * *

EXHIBIT 3

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 4,933,456

DATED : June 12, 1990

INVENTOR(S) : Scott M. ROCKLAGE and Steven C. QUAY

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Col. 25, lines 46-47 (Claim 1); delete "CH" appended to the left-handed pyridine ring, in the position meta to the pyridyl nitrogen, and replace with --OH--.

Signed and Sealed this

Twelfth Day of October, 1993

Attest:

Attesting Officer

BRUCE LEHMAN

Commissioner of Patents and Trademarks

EXHIBIT 3

EXHIBIT 4

Patent Maintenance Fees - Public Inquiry

Patent#: 4933456 Filed: 05/08/87 Issued: 06/12/90 Serial#: 07047614
Status: 12th Year Fee Window Opens: 06/12/01
Window Opens: 06/12/01 Surchg Due: 12/12/01 Sml Entity: NO
Fee Amt Due:$ 3160 Surchg Amt Due:$ Expiration: 06/12/02
Fee Code: 185 Surchg Code: Total Amt Due:$ 3160
Title: DIPYRIDOXYL PHOSPHATE NMRI CONTRAST AGENTS

Address For Fee Purposes:
BARRY E. BRETSCHNEIDER
FISH & RICHARDSON
601 THIRTEENTH STREET, N.W.
WASHINGTON DC 20005-4004

Most Recent Significant Events:

12/08/97	Payment of Maintenance Fee, 8th Year, Large Entity
07/25/96	Payor Number Assigned
01/10/94	Pat Hldr no Longer Claims Small Ent Stat as Small Business
12/22/93	Surcharge for Late Payment, Large Entity
12/22/93	Payment of Maintenance Fee, 4th Year, Large Entity
	Last Event On Maintenance History

EXHIBIT 4

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
ASSISTANT SECRETARY AND COMMISSIONER
OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

DATE MAILED
01/09/1998

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633 WEST 5TH STREET
SUITE 4700
LOS ANGLES CA 90071-2066

In response to your communication of 01/09/1998 concerning the status of payment of maintenance fees due, the following is provided:

Patent Number	: 4933456
Application Serial Number	: 07/047,614
Application Filing Date	: 05/08/1987
Issue Date	: 06/12/1990

Status: 12TH YEAR FEE WINDOW OPENS: 06/12/2001

(PTOL-438)

EXHIBIT 5A

BRIEF DESCRIPTION OF SIGNIFICANT ACTIVITIES: IND LOG

WIN Number: 59010
Common Drug Name: TESLASCAN
IND Number: 33031
IND Description: MRI - LIVER LESIONS -INJ

Date(s): (01-JAN-55 -> 01-JAN-99)
Subject: (%)
Communication Type: (%)

Date	Comm.Type	Serial No.	Location	Abstract
02-FEB-89	LTF		V-1	SUBMITTED INFORMATION PACKAGE FOR PRE-IND, MEETING AND CONFIRMED THE MEETING DATE OF 10-MAR-89. CC: PE+(SOUS) SA+(NYCOMED) RJ+(S/W)
10-MAR-89	MOM		V-1	FDA MEMO OF PRE-IND MEETING HELD 10-MAR-89, IN WHICH CMC AND PRECLINICAL TOXICOLOGY ISSUES WERE DISCUSSED. CC: CRB EHC AF JF SAG HG ARN HCP FJR JS RS JS JGT
10-MAR-89	MOM		V-1	STERLING'S MEETING MINUTES OF 10-MAR-89. CC: PE+(SOUS) SA+(NYCOMED) RJ+(S/W)
04-APR-89	SUB	000	V. 2-6	SUBMITTED INITIAL IND APPLICATION. (PE+(SOUS) SA+(NYCOMED) RJ+(S/W)-VOL. 1 ONLY)
10-APR-89	LFF		V-7	FDA ACKNOWLEDGED RECEIPT OF IND SUBMISSION, AND ASSIGNED IND NUMBER 33,031. CC: PE(SOUS) SA(NYCOMED) RJ(S/W)
10-APR-89	LTF		V-7	SUBMITTED REVISED CREATININE CLEARANCE, VALUES IN TABLE C OF THE PHASE I PROTOCOL IN THE ORIGINAL IND SUBMISSION AND A REPLACEMENT PAGE FOR A TYPOGRAPHICAL ERROR IN THE UROBILINOGEN NORMAL RANGE VALUE. CC: SALUTAR(JM MO SQ MVW)
10-APR-89	TEL		V-7	FDA INFORMED RE: REVISION TO CREATININE, CLEARANCE SUBSTANTIAL CHANGE VALUE IN TABLE C OF THE PHASE I PROTOCOL. MS. LANGE REQUESTED THREE COPIES OF THE REPLACEMENT PAGES BE SENT DIRECTLY TO HER SO SHE COULD REPLACE THE PAGES IN THE FDA'S THREE IND COPIES. CC: SALUTAR(RB BD GJ JM MO SQ SR MVW)
17-APR-89	TEL		V-7	INFORMED FDA OF MINOR INCONSISTENCIES, BETWEEN THE DRAFT MEETING MINUTES PROVIDED BY THE FDA AND SALUTAR'S IN-HOUSE MEETING MINUTES. FDA SUGGESTED THAT IT WOULD BE SUFFICIENT TO HIGHLIGHT THE AREAS IN QUESTION AND TO PROVIDE HANDWRITTEN COMMENTS ON THE DRAFT MINUTES. AFTER RECEIVING AND REVIEWING THE CHANGES, FDA WOULD INFORM DRA OF THE RESULTS. CC: SALUTAR(RB JM MO SQ SR MVW)

EXHIBIT 5A

IND LOG

WIN Number: 59010
Common Drug Name: TESLASCAN
IND Number: 33031
IND Description: MRI - LIVER LESIONS -INJ

Date(s): (01-JAN-55 -> 01-JAN-99)
Subject: (%)
Communication Type: (%)

Date	Comm.Type	Serial No.	Location	Abstract
17-APR-89	TEL		V-7	SA(NYCOMED) PE(SOUS) RJ(S/W)
18-APR-89	LTF		V-7	SUBMITTED COMMENTS ON THE PRE-IND MEETING, MINUTES AND PROPOSED REVISIONS. CC: SALUTAR(JM) PE(SOUS) RJ(S/W) SA(NYCOMED)
25-APR-89	TEL		V-7	DRA INQUIRY RE: COMMENTS ON PRE-IND, MEETING MINUTES. DRA INFORMED THAT THE MEETING MINUTES WERE ACCEPTABLE AS REVISED. DISCUSSED REVISIONS TO THE PHASE I PROTOCOL. CC: SALUTAR(RB JM MO SQ SR MVW) SA(NYCOMED) RJ(S/W) PE(SOUS)
28-APR-89	LTF		V-7	SUBMITTED AMENDED STUDY PLAN FOR PHASE I, PROTOCOL WHICH HAS BEEN REVISED TO CLARIFY THE BLINDING PROCEDURE. THE WEEKLY SCHEDULE OUTLINED IN THE STUDY PLAN HAS BEEN MODIFIED TO ALLOW THE OPTION OF IMAGING TWO SUBJECTS ON A FRIDAY OR A WEEKEND DAY. CC: SALUTAR(JM SQ SR)
28-APR-89	TEL		V-7	INFORMED FDA THAT PHASE I PROTOCOL CHANGES, WERE SENT TO THE FDA VIA FEDERAL EXPRESS. CC: SALUTAR(MB MO SQ SR MVW)
04-MAY-89	TEL		V-7	DR. MACHURU CALLED RE: PHASE I CLINICAL, TRIALS. INFORMED SALUTAR THAT THE IND DID NOT CONTAIN ANY INFORMATION THAT THE CHELATE IS FORMED AND THAT IT EXISTS AS THE MEGLUMINE SALT. FDA REQUESTED CERTIFICATES OF ANALYSIS FOR SPECIFIC LOTS AND THAT EPR SPECTRA BE SUBMITTED FOR SPECIFICALLY NAMED MATERIALS (04-MAY-89). INFORMATION WAS FAXED ON 05-MAY-89. FDA AGREED TO THE INITIATION OF THE CLINICAL STUDY PROVIDED THE SAFETY DATA ON THE FIRST GROUP IS SUBMITTED AS SOON AS POSSIBLE. CC: SALUTAR(KB BD GJ SQ SR) NYCOMED(TJ SA) STERLING(DMB) PE(SOUS) RJ(S/W)
05-MAY-89	LTF		V-7	SUBMITTED CERTIFICATES OF ANALYSIS AND EPR, SPECTRA ON SPECIFIED MATERIALS THE FDA REQUESTED ON 04-MAY-89. CC: SALUTAR(KB GJ SQ SR) STERLING(DMB) NYCOMED(TJ SA) PE(SOUS) RJ(S/W)

IND LOG

WIN Number: 59010
Common Drug Name: TESLASCAN
IND Number: 33031
IND Description: MRI - LIVER LESIONS -INJ

Date(s): (01-JAN-55 -> 01-JAN-99)
Subject: (%)
Communication Type: (%)

Date	Comm.Type	Serial No.	Location	Abstract
05-MAY-89	SUB	001	V-7	INFO. AMEND: CMC WHICH INCLUDES ADDITIONAL, STABILITY DATA OUT TO 12 MONTHS. BASED ON THIS DATA THE EXPIRATION DATE ON LOT NO. SQ-12-01278 IS EXTENDED TO 18 MONTHS. NEW LOTS FOR THE CLINICAL TRIALS WILL ALSO HAVE AN 18 MONTH EXPIRATION DATE. ALSO SUBMITTED A REVISED STABILITY TESTING AND SAMPLING SCHEDULE FOR LOT NO. SQ-12-01278 WHICH REPLACES THE SCHEDULE IN THE ORIGINAL IND APPEARING IN VOLUME 1 ON PAGE 318. CC: SALUTAR(KB RB SQ SR) STERLING(DMB) NYCOMED(TJ SA) PE(SOUS) RJ(S/W)
10-MAY-89	LTF		V-7	SUBMITTED DATA ON THE FIRST SIX SUBJECTS, IN GROUP A FROM THE PHASE I STUDY SAL-095-1011 PER REQUEST FROM THE FDA ON 04-MAY-89. THE FOLLOWING INFORMATION IS INCLUDED: DEMOGRAPHIC, VITAL SIGNS, ELECTROCARDIOGRAM, LABORATORY EVALUATIONS, INJECTION SITE DISCOMFORT, AND ADVERSE EVENTS. CC: SALUTAR(JM MO SQ SR MVW) STERLING(DMB) NYCOMED(TJ)
11-MAY-89	TEL		V-7	FDA DISCUSSED DATA FROM THE FIRST SIX, SUBJECTS ON THE PHASE 1 STUDY. PERMISSION TO PROCEED WITH THE PHASE I STUDY WAS GRANTED PROVIDED SAFETY INFORMATION AFTER EACH DOSAGE GROUP WAS SENT TO THE FDA. CC: SALUTAR(JM MO SQ SR MVW)
18-MAY-89	LTF		V-7	SUBMITTED PRELIMINARY SAFETY INFORMATION, FOR SUBJECTS FROM GROUPS A (3 MOL/KG) AND B (10 MOL/KG) IN THE PHASE I STUDY SAL-095-1011. CC: SALUTAR(JM SQ SR MVW)
30-MAY-89	TEL		V-7	FDA COMMENTED ON THE GROUP A AND B SAFETY, DATA, AND GRANTED PERMISSION FOR DOSING OF SUBJECTS IN GROUP D. CC: SALUTAR(JM MO SQ SR MVW)
02-JUN-89	LTF		V-7	PC: SAL-095-1011-1; SUBMITTED 24-HOUR SAFETY, INFORMATION ON THE FIRST SIX SUBJECTS (017-022) IN GROUP C FOR SAL-095-1011-3. THE AMENDED PROTOCOL CHANGED THE GROUP C DOSAGE AND ADMINISTRATION RATE TO 10 MOL/KG, INFUSED INTRAVENOUSLY AT 0.08 ML/SEC; AND TO ALLOW GROUP D SUBJECTS TO RECEIVE EITHER PLACEBO OR S-095 INJECTION AT A DOSAGE OF

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02-JUN-89	LTF		V-7	15 MOL/KG INFUSED INTRAVENOUSLY AT A RATE OF 0.12 ML/SEC. DR. LEESE FOR PROTOCOL SAL-095-1011-1. (SEE DR. CHOW'S REQUEST IN CONTACT REPORT DATED 30-MAY-89.) CC: SALUTAR(JM MO SQ SR MVW)
08-JUN-89	LTF		V-7	PC/NI: SAL-095-1011-2; SUBMITTED 24-HOUR, SAFETY INFORMATION ON THE FIRST SIX SUBJECTS (025-030) IN GROUP D FOR SAL-095-1011-4. THIS PROTOCOL WAS AMENDED 02-JUN-89 TO CHANGE THE GROUP D DOSAGE AND ADMINISTRATION RATE TO 15 MOL/KG, INFUSED INTRAVENOUSLY AT 0.12 ML/SEC. THE PHASE I PROTOCOL HAS ALSO BEEN AMENDED TO ALLOW GROUP E SUBJECTS TO RECEIVE EITHER PLACEBO OR S-095 INJECTION AT A DOSAGE OF 20 MOL/KG, INFUSED INTRAVENOUSLY AT A RATE OF 0.16 ML/SEC. DR. LEESE WILL BE USING SAL-095-1011-2. (SEE DR. CHOW'S REQUEST IN CONTACT REPORT DATED 30-MAY-89.) CC: SALUTAR(JM MO SQ SR MVW)
15-JUN-89	TEL		V-7	FDA INFORMED DRA THAT A DEFICIENCY LETTER, WAS DRAFTED AND WOULD BE SENT SHORTLY. CC: SALUTAR(JM MO SQ SR MVW) PE(SOUS) RJ(S/W) SA(NYCOMED)
19-JUN-89	SUB	002	V-7	PC/NI: SAL-095-1011-3, SAL-095-1011-4, SAL-095-1011-5, SAL-095-1011-6. SAL-095-1011-3 CHANGES THE GROUP C DOSAGE AND ADMINISTRATION RATE TO 10 MOL/KG, INFUSED INTRAVENOUSLY AT 0.08 ML/SEC. WITH A VOLUME OF 0.069 ML/KG. SAL-095-1011-4 CHANGES THE GROUP D DOSAGE AND ADMINISTRATION RATE TO 15 MOL/KG, INFUSED INTRAVENOUSLY AT 0.12 ML/SEC WITH A VOLUME OF 0.104 ML/KG. SAL-095-1011-5 CHANGES THE GROUP E DOSAGE AND ADMINISTRATION RATE TO 20 MOL/KG, INFUSED INTRAVENOUSLY AT 0.16 ML/SEC WITH A VOLUME OF 0.138 ML/KG. SAL-095-1011-6 CHANGES GROUP F DOSAGE AND ADMINISTRATION RATE TO 25 MOL/KG, INFUSED INTRAVENOUSLY AT 0.2 ML/SEC WITH A VOLUME OF 0.172 ML/KG. DR. LEESE WILL BE USING ALL PROTOCOLS. CC: SALUTAR(JM MO SQ SR MVW)
20-JUN-89	SUB	003	V-7	SUBMITTED SAFETY INFORMATION ON THE FIRST, SIX SUBJECTS (033-038) IN GROUP E OF THE PHASE I STUDY. ALSO SUBMITTED CLINICAL LABORATORY RESULTS FOR GROUP C AND

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20-JUN-89	SUB	003	V-7	GROUP D SUBJECTS UP THROUGH THE 72 HOUR POST TEST ARTICLE ADMINISTRATION TIME POINT. CC: SALUTAR(JM MO SQ SR MVW)
21-JUN-89	TEL		V-7	DRA INQUIRED AS TO STATUS OF THE DEFICIENCY, LETTER. FDA TRYING TO CLARIFY COMMENTS CONCERNING THE CMC SECTION AND HOPED THAT A DRAFT LETTER WOULD BE READY BY THE END OF THE WEEK. CC: SALUTAR(JM MO SQ SR MVW) RJ(S/W) PE(SOUS) SA(NYCOMED)
05-JUL-89	SUB	004	V-7	SUBMITTED SAFETY INFORMATION ON SUBJECTS, (41-46) IN GROUP F FOR SAL-095-1010-6. CC: SALUTAR(JM MO SQ SR MVW) STERLING(DMB)
07-JUL-89	SUB	005	V-7	PC: SAL-095-1011-7 ADDS AN ADDITIONAL, DOSAGE GROUP G TO RECEIVE A DOSAGE OF 10 MOL/KG OR PLACEBO, ADMINISTERED AS AN INTRAVENOUS INFUSION AT A RATE OF 0.016 ML/SEC. OVER APPROXIMATELY 5 MINUTES. GROUP G WILL CONTAIN TEN SUBJECTS. THE TEN SUBJECTS WILL BE ADMINISTERED S-095 OR PLACEBO. FOUR SUBJECTS WILL RECEIVE S-095 AND TWO WILL RECEIVE PLACEBO. THE REMAINING FOUR SUBJECTS WILL RECEIVE S-095 AND WILL UNDERGO IMAGING PRE- AND POST-ADMINISTRATION. DR. LEESE FOR SAL-095-1011-8. CC: SALUTAR(JM MO SQ SR MVW) STERLING(DMB)
12-JUL-89	LFF		V-7	FDA REVIEWED IND AND SUBMITTED REQUESTS, AND RECOMMENDATIONS CONCERNING THE CMC AND PHARMACOLOGY SECTIONS. FDA ALSO REQUESTED ADDITIONAL INFORMATION TO THE UPDATED SAFETY REPORTS WHICH WERE SUBMITTED FOR REVIEW. THE REVISIONS TO THE MINUTES OF THE PRE-IND MEETING HAVE BEEN APPROVED BY ALL THE INVOLVED FDA ATTENDEES OF THAT MEETING AND ARE AGREED UPON AS REVISED. CC: PE(SOUS) SA(NYCOMED) RJ(S/W)
13-JUL-89	TEL		V-7	SALUTAR REQUESTED STATUS OF THE DEFICIENCY, LETTER. SALUTAR WAS INFORMED THAT THE LETTER WAS IN REVIEW AND THAT THE LETTER WOULD INCLUDE A STATEMENT FROM FDA INDICATING THAT THEY AGREED WITH SALUTAR'S COMMENTS ON THE PRE-IND MEETING MINUTES. FDA STATED THAT THEY WOULD FAX

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13-JUL-89	TEL		V-7	THE DEFICIENCY LETTER AFTER REVIEW. CC: SALUTAR(JM MO SQ SR MV)
20-JUL-89	TEL		V-7	SALUTAR REQUESTED CLARIFICATION OF ITEM 2.F., OF THE DEFICIENCY LETTER AND TO OBTAIN A COPY OF THE REVIEWER'S NOTES RE: THE MAGNEVIST SUPPLEMENT. FDA TO RETURN CALL WITH A RESPONSE. CC: SALUTAR(JM MO SQ SR MV) PE(SOUS) SA(NYCOMED) RJ(S/W)
21-JUL-89	TEL		V-7	FDA CALLED TO DISCUSS ITEM 2.F. OF THE, DEFICIENCY LETTER AND SALUTAR'S REQUEST FOR THE FDA REVIEWS OF THE MAGNEVIST SUPPLEMENT. SALUTAR INFORMED TO SPEAK DIRECTLY WITH DR. PAT MATURU RE: ITEM 2.F. AND THAT THE FDA WOULD FORWARD THE INFORMATION REQUESTED BY SALUTAR WITHIN TWO WEEKS RE: THE MAGNEVIST SUPPLEMENT. CC: SALUTAR(JM SQ SR) PE(SOUS) SA(NYCOMED) RJ(S/W)
11-AUG-89	SUB	006	V-7	INFO. AMEND: CLINICAL, NEW SUBINVESTIGATORS, DRS. PFEFFERBAUM AND LIM FOR PROTOCOL SAL-095-1011 AND SAL-095-1011-1/2/3/4/5/6/8 DR. LEESE'S STUDY. SUBMITTED SAFETY INFORMATION ON SUBJECTS (49-54) IN GROUP G. CC: SALUTAR(JM MO SQ SR MVW)
22-SEP-89	TEL		V-7	FDA QUESTIONED THE APPLICATION REQUESTING, APPROVAL TO EXPORT S-095 INJECTION TO GERMANY FOR USE IN CLINICAL INVESTIGATIONS. SALUTAR STATED THAT S-095 INJECTION WOULD BE USED VIA THE SAME DOSAGE ROUTE AND EVALUATED FOR USE IN CONJUNCTION WITH MRI OF THE HEPATOBILIARY SYSTEM. SINCE THIS IS THE CASE, FDA STATED THAT THEIR DIVISION DID NOT HAVE A PROBLEM WITH THE EXPORT REQUEST. CC: SALUTAR(JM SQ SR)
09-JAN-90	SUB	007	V-7	RESPONSE TO INFORMATION REQUEST OF 17-JUL-89, WHICH ADDRESSES CHEMISTRY AND PHARMACOLOGY CONCERNS AND ISSUES RAISED BY THE FDA. CC: SALUTAR(KB BD GJ MO SQ SR) STERLING(DMB) NYCOMED(SA AB AM RK PS EH OS) DAIICHI(YN) PE(SOUS) SA(NYCOMED) RJ(S/W)

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27-FEB-90	TEL		V-7	SALUTAR QUESTIONED THE STATUS OF THEIR, RESPONSE TO THE DEFICIENCY LETTER SUBMITTED ON 09-JAN-90. FDA IS CURRENTLY REVIEWING SALUTAR'S COMMENTS AND WILL CALL BACK WITH THE STATUS. CC: SALUTAR(BD GJ JM SQ SR MV) PE(SOUS) SA(NYCOMED) RJ(S/W)
02-MAR-90	TEL		V-7	FDA INFORMED DRA THAT SALUTAR'S DEFICIENCY, LETTER RESPONSES WERE CURRENTLY BEING CONSOLIDATED BY DR. SALAZAR, A NEW REVIEWING CHEMIST UNDER DR. SHEININ. CC: SALUTAR(JM SQ SR) PE(SOUS) SA(NYCOMED) RJ(S/W)
04-APR-90	SUB	008	V.8-9	NP: 095-1145; NI; INFO. AMEND: CLINICAL, DRS. BERNARDINO, YOUNG, LEE, AND WEINREB FOR PROTOCOL 095-1145. SUBMITTED PROPOSED CLINICAL PLAN, DRAFT PHASE II PROTOCOL, AND PHASE I CLINICAL STUDY REPORT. REQUESTED AN END-OF-PHASE I MEETING.
16-APR-90	TEL		V-10	DRA INQUIRY RE: STATUS OF CMC AMENDMENT, DATED 09-JAN-90. FDA REMINDED THAT THE DEFICIENCY LETTER OF 12-JUL-89 PRECLUDED PROCEEDING WITH PHASE II UNTIL THE FDA WAS SATISFIED ON THE CHEMISTRY QUESTIONS. DRA INFORMED THAT THE AMENDMENT REVIEW SHOULD BE COMPLETED WITHIN TWO WEEKS. CC: SALUTAR(KB BC SQ SR MVW) STERLING(DMB ARN) NYCOMED(TJ SA) RJ(S/W) PE(SOUS)
01-MAY-90	TEL		V-10	SRG INQUIRY RE: STATUS OF CMC AMENDMENT, OF 09-JAN-90 AND CLINICAL AMENDMENT OF 04-APR-90. FDA CHEMIST (DR. SALAZAR) PROVIDED A LIST OF REQUESTS AND QUESTIONS ABOUT THE CMC AMENDMENT. CC: SALUTAR(KB RB BC BD GJ SQ SR) STERLING(DMB HH ARN) NYCOMED(RK TT SA) DAIICHI(YN) BYK BULDEN(KS) PE(SOUS) RJ(S/W)
04-MAY-90	TEL		V-10	FDA INFORMED DRA THAT DR. JONES HAD, COMPLETED HIS REVIEW OF THE CLINICAL AMENDMENT OF 04-APR-90 AND AGREED THAT A MEETING WAS APPROPRIATE. TENTATIVELY SCHEDULED MEETING FOR 24-MAY-90. FDA REQUESTED A DETAILED AGENDA AND COPIES OF ANY OVERHEAD PROJECTS TO BE USED. DR. JONES HAD FOUND IN READING THE AMENDMENT A REFERENCE ON

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04-MAY-90	TEL		V-10	PAGE 195 TO AN ATTACHMENT WHICH HE COULD NOT FIND. HE REQUESTED HELP IN LOCATING IT, OR FOR DRA TO PROVIDE A COPY OF IT FOR HIS REVIEW. CC: SALUTAR(KB SQ SR MVW)
09-MAY-90	TEL		V-10	DRA CONFIRMED 18-JUN-90 MEETING WITH THE FDA. CC: SALUTAR(KB SQ SR MVW) STERLING(DMB HH ARN) NYCOMED(TT)
11-MAY-90	SUB	009	V-10	RESPONSE TO INFORMATION REQUEST BY, DR. JONES (SEE CONTACT REPORT DATED 04-MAY-90). SUBMITTED THE ATTACHMENT REFERENCED ON PAGE 195 OF THE AMENDMENT DATED 09-APR-90.
18-MAY-90	TEL		V-10	SRG PROVIDED WITH THE FOLLOWING, INFORMATION ABOUT THE 18-JUN-90 MEETING. . DR. JONES AGREES THAT THE PHASE II STUDY MAY PROCEED (RECOGNIZE THAT DR. JONES IS UNAWARE OF THE SITUATION WITH THE MANUFACTURING AND CONTROL QUESTIONS). . THE DATA ARE NOT ARRAYED IN A MANNER TO PERMIT EASY REVIEW. FDA ASKS THAT THE PHASE I DATA BE ARRAYED BY PATIENT AND REFERRED TO THE GUIDELINES FOR CLINICAL AND STATISTICAL REPORTS, PAGES 76-80. . THE FIELD STRENGTH IS NOT SPECIFIED ON PAGES 18 & 19 AS IT SHOULD BE. . SERUM IRON SHOULD BE ADDED ON PAGE 21. CC:SALUTAR(KB SQ SR MVW) STERLING(DMB HH ARN) NYCOMED(RK TT)
23-MAY-90	SUB	010	V-10	PC/NI(4):095-1145,A-01 DELETES THE VITAL, SIGNS MEASUREMENTS AT '60 MINUTES AFTER THE PROCEDURE' AND CHANGES THE VITAL SIGNS MEASUREMENTS FROM '2 HOURS AFTER THE PROCEDURE' TO '2 HOURS AFTER THE START OF INJECTION.' NI: DRS. BERNARDINO, YOUNG, LEE & WEINREB FOR 095-1145,A-01. CC: SALUTAR(JM SQ SR MVW) BYK GULDEN(DR. SHICK) DAIICHI(YN) NYCOMED(SA) STERLING(DMB)
31-MAY-90	TEL		V-10	FDA INFORMED THAT SUBMISSION OF 23-MAY-90, SHOULD BE SUBMISSION 010 NOT 009 AS NOTED ON THE SUBMISSION. CC: SALUTAR(JM SQ SR) STERLING(DMB HH ARN) NYCOMED(RK TT)

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01-JUN-90	TEL		V-10	DRA INQUIRED IF END-OF-PHASE I MEETING, WITH FDA WAS NECESSARY. FDA DID NOT SEE A NEED TO MEET, AND STATED THAT THEIR QUESTIONS CONCERNING THE PHASE II STUDY COULD BE ADDRESSED IN PROTOCOL AMENDMENTS. DR. JONES' COMMENTS ON THE PHASE II PROTOCOL WHICH WERE VERBALLY RELAYED TO JIM MUTCH ON 21-MAY-90 WOULD BE FORMALIZED IN A LETTER SENT TO DRA WITHIN TWO WEEKS. CC: SALUTAR(JM SQ SR) STERLING(DMB HH ARN) NYCOMED(RK TT SA) PE RJ(SANOFI)
12-JUN-90	FAC		V-10	DR. CHOW'S (FDA) CHEMISTRY DEFICIENCY, PROBLEM LIST WAS FAXED TO DRA. COMMENTS AND RECOMMENDATIONS ARE NOTED.
12-JUN-90	TEL		V-10	DRA INQUIRY RE: DRAFT COPY OF FDA'S COMMENTS, ON THE PHASE I STUDY REPORT AND PHASE II PROTOCOL. FDA WILL SEND THE DRAFT COPY VIA TELEFAX. DRA RECONFIRMED THAT THE PHASE II STUDY COULD PROCEED PROVIDED THAT SALUTAR ADEQUATELY RESPOND TO THE CHEMISTRY ISSUES. CC: NYCOMED(RK TJ) SALUTAR(JM SQ SR MVW) STERLING(DMB HH ARN)
21-JUN-90	SUB	011	V-10	NI/PC: 095-1145,A-02 WHICH HAS BEEN REVISED, AS FOLLOWS: SECTION 5.2 EFFICACY HAS BEEN REVISED TO ADDRESS THE FIELD STRENGTH OF THE MAGNET USED, AND SECTION 5.3.2 HAS BEEN REVISED TO INCLUDE 'IRON' IN THE LIST OF SERUM CHEMISTRY PARAMETERS TO BE ANALYZED. DRS. BERNARDINO, YOUNG, LEE AND WEINREB FOR PROTOCOL 095-1145,A-02. CC: SALUTAR(JM SR MVW) BYK GULDEN(DR. SHICK) DAIICHI(YN) NYCOMED(SA) STERLING(DMB)
03-JUL-90	SUB	012	V-10	RESPONSE TO INFORMATION REQUEST OF, DR. SALAZAR DATED 01-MAY-90. CHEMISTRY QUESTIONS RAISED BY DR. SALAZAR AND SALUTAR'S RESPONSES ARE INCLUDED. CC: SALUTAR(BD GJ JM SR MVW DW) BYK GULDEN(DR. SHICK) DAIICHI(YN) NYCOMED(SA) STERLING(DMB) PE(SOUS) RJ(S/W)
20-JUL-90	TEL		V-10	DRA INQUIRY RE: STATUS OF CMC RESPONSES, SUBMITTED TO DR. SALAZAR ON 03-JUL-90. DR. SALAZAR HAS NOT COMPLETED HER REVIEW. SALUTAR SHOULD NOT PROCEED WITH THE

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20-JUL-90	TEL		V-10	PHASE II STUDY UNTIL THE CHEMISTRY REVIEW IS COMPLETED. CC: SALUTAR(BD GJ JM SR MVW DW) STERLING(DMB) NYCOMED(RK TT SA) PE(SOUS) RJ(S/W)
06-AUG-90	TEL		V-10	DRA INQUIRY RE: STATUS OF CHEMISTRY RESPONSES, SENT TO DR. SALAZAR. REVIEW IS NOT COMPLETED YET. CC: SALUTAR(JM SR MVW) STERLING(DMB HH) NYCOMED(RK TT SA) PE(SOUS) RJ(S/W)
10-AUG-90	SUB	013	V-11	PC(2)/INFO.AMEND:CLINICAL/RIR/NI(4):PROTOCOL, 095-1145,A-03 & 095-1145,A-04. 095-1145,A-03 PROVIDES FOR MINOR CHANGES TO THE TEXT OF THE INVESTIGATIONAL DRUG LABEL. 095-1145,A-04 PROVIDES FOR CHANGES IN THE MONITORING OF VITAL SIGNS. INFORMATION AMENDMENT - CLINICAL PROVIDES THE QUALIFICATIONS FOR THE CLINICAL MONITOR AND PRINCIPAL INVESTIGATORS OF THE PHASE II CLINICAL STUDY. INFORMATION WAS SUPPLIED IN RESPONSE TO THE FDA DRAFT CORRESPONDENCE DATED 12-JUN-90 CONCERNING THE S-095 INJECTION PHASE II CLINICAL PROTOCOL (095-1145) AND THE S-095 INJECTION PHASE I CLINICAL REPORT (SAL-095-1011). DRS. BERNARDINO, YOUNG, LEE & WEINREB AS PRINCIPAL INVESTIGATORS FOR 095-1145 AND AMENDMENTS A-01, A-02, A-03 & A-04. CC: SALUTAR(JM SR MV AW) BYK GULDEN(DR. SCHICK) DAIICHI(YN) NYCOMED(SA) STERLING(DB)
15-AUG-90	TEL		V-11	FDA CONTACTED RE: CHEMISTRY RESPONSE STATUS, FDA IS WAITING TO OBTAIN INFORMATION RE: WATER AND PLASMA RELAXIVITY VALUE CALCULATIONS USING THE NONLINEAR REGRESSION TECHNIQUE; AND, AN EXPLANATION AS TO WHY THE WATER RELAXIVITY VALUES WERE THE SAME WHEN DETERMINED USING BOTH THE LINEAR AND NONLINEAR MODELS. SALUTAR STATED THAT THIS INFORMATION IS NOT AN ISSUE RELATED TO SAFETY; THEREFORE, THE PHASE II STUDIES SHOULD BE ABLE TO PROCEED. FDA HELD A MEETING TO DISCUSS THIS ISSUE AND CONTACTED SALUTAR ON 16-AUG-90 TO STATE THAT NOTIFICATION FOR PHASE II STUDIES SHOULD BE RECEIVED BY MID-WEEK NEXT WEEK. CC: SALUTAR(JM SR MV) STERLING(DB HH GK) NYCOMED(RK TT SA) PE(SOUS) RJ(S/W)
24-AUG-90	SUB	014	V-11	INFO.AMEND: CMC; BASED ON STABILITY,

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24-AUG-90	SUB	014	V-11	INFORMATION, THE EXPIRATION DATING ON TWO LOTS WILL BE INCREASED FROM 18 MONTHS TO 30 MONTHS. NEW LOTS MANUFACTURED FOR CLINICAL TRIALS WILL ALSO HAVE 30 MONTH EXPIRATION DATING. CC: SALUTAR(KB SR AW) BYK GULDEN(DR. SCHICK) DAIICHI(YN) NYCOMED(SA TT) STERLING(DB DK NA GG WG WH PH) PE(SOUS) RJ(S/W)
24-AUG-90	TEL		V-11	FDA STATED THAT PHASE II STUDIES CAN PROCEED, EVEN THOUGH MINOR CMC QUESTIONS ARE STILL OUTSTANDING. THOSE QUESTIONS TO BE COMMUNICATED IN THE NEAR FUTURE. CC: SALUTAR(KB BC BD SR MV AW) STERLING(DB PH) NYCOMED(TT SA) PE(SOUS) RJ(S/W)
13-NOV-90	SUB	015	V-12	ANNUAL REPORT: 05-APR-89 THROUGH 04-APR-90, PLUS FOUR FINAL PRECLINICAL STUDY REPORTS. REVISED INVESTIGATOR'S BROCHURE. CC: SALUTAR(KB SR AW) BYK GULDEN(DR. SCHICK) DAIICHI(YN) NYCOMED(SA) STERLING(DB)
04-DEC-90	SUB	016	V-13	SAFETY REPORT PERTAINING TO THE DEATH, OF A PATIENT ENROLLED IN PROTOCOL 095-1145. THE INVESTIGATOR DETERMINED NO DIRECT RELATIONSHIP BETWEEN THE PATIENT'S DEMISE AND THE DRUG.
17-JAN-91	SUB	017	V-13	NSI(2): DRS. HODGES & THOMPSON TO 095-1145, & AMENDMENTS A-01, A-03 & A-04 FOR DR. BERNARDINO. CC: STERLING(DMB) NYCOMED(TT)
15-MAR-91	TEL		V-13	FDA WAS ASKED TO FORWARD A COPY OF CHEMISTRY, REVIEWERS COMMENTS RE: FEW MINOR OUTSTANDING ISSUES. SINCE THE ISOLATED DRUG SUBSTANCE ROUTE IS BEING PURSUED, THE FDA ISSUES MAY NOT BE APPLICABLE. SALUTAR REQUESTED THE CHEMISTRY COMMENTS PRIOR TO END OF PHASE II MEETING. CC: SALUTAR(KB AC JM SR) STERLING(DB HH) NYCOMED(TT SA) PE(SOUS) RJ(S/W)
03-APR-91	TEL		V-13	FDA STATED THAT AN ASEPTICALLY PROCESSED, SINGLE DOSE PRODUCT THAT COULD NOT BE TERMINALLY STERILIZED WAS NOT REQUIRED TO CONTAIN A PRESERVATIVE. FDA IS

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03-APR-91	TEL		V-13	DEVELOPING AN INTERNAL POLICY REQUESTING COMPANIES TO 1) PROVIDE DATA TO DEMONSTRATE THAT THE PRODUCT IN QUESTION COULD NOT BE TERMINALLY STERILIZED AND, 2) TO PROVIDE A VALIDATION PACKAGE. ITEM NO. 1 SHOULD BE PROVIDED AT THE IND AND NDA STAGES AND ITEM NO. 2 AT THE NDA STAGE. CC: SALUTAR(BD BC AC JM DN SR) STERLING(DB HH GK) NYCOMED(TT SA) PE(SOUS) RJ(S/W)
24-JUN-91	SUB	018	V-14	ANNUAL REPORT: 05-APR-90 THROUGH 04-APR-91, INFO.AMEND: PHARM/TOX CONTAINING 4 PRECLINICAL REPORTS AND THREE SUMMARIES OF PRECLINICAL STUDIES CONDUCTED BY BYK GULDEN IN GERMANY.
17-SEP-91	SUB	019	V-14	SAFETY REPORT (PRECLINICAL) FOR STUDY NO., PH 328-SA-001-90. MAJOR ADVERSE REPRODUCTIVE EFFECTS ON RATS.
23-SEP-91	SUB	020	V-14	FDA NOTIFIED OF TRANSFER OF OWNERSHIP, FROM SALUTAR TO STERLING DRUG INC. EFFECTIVE 20-SEP-91. CC: SA(NYCOMED) PE(SOUS) RJ(S/W)
27-SEP-91	SUB	021	V-14	INFORMED FDA OF SRG'S ACCEPTANCE, OF THE TRANSFER OF IND 33,031 FROM SALUTAR EFFECTIVE 20-SEP-91. CC: PROJECT TEAM (SA(NYCOMED)) DB EHC JFF JF HH MK AN OWW+ FJR PS PE(SOUS) RJ(S/W)
13-MAR-92	SUB	022	V-14	FDA NOTIFIED OF CHANGE IN MEDICAL MONITOR; MICHAEL KITT IS RESPONSIBLE FOR MONITORING THE CONDUCT AND PROGRESS OF THE CLINICAL INVESTIGATIONS UNDER THIS IND. CAROLYN PARADISE IS RESPONSIBLE FOR REVIEWING AND EVALUATING THE SAFETY IN INVESTIGATIONS CONDUCTED UNDER THIS IND. JOHN FRANK IS NO LONGER INVOLVED IN THE CONDUCT OF STUDIES UNDER THIS IND. CC: PROJECT TEAM (SA(NYCOMED)) DB JFF HH MK AN OWW CP FJR PS
13-MAR-92	SUB	023	V-14	FDA NOTIFIED OF CORPORATE NAME CHANGE TO, STERLING WINTHROP INC. ALSO, THE RESEARCH ORGANIZATION IS NOW STERLING WINTHROP PHARMACEUTICALS RESEARCH DIVISION.

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13-MAR-92	SUB	023	V-14	CC: PROJECT TEAM (SA(NYCOMED)) DB JFF HH MK AN OWW CP FJR PS
09-APR-92	TEL		V-14	SWPRD REQUESTED THE END OF PHASE II MEETING, TO COINCIDE WITH IODIXANOL PRE-NDA MEETING, WEEK OF 08-JUN-92 IF POSSIBLE. CC: PROJECT TEAM DB PC EHC JFF DJF MMK NDL PM OWW CMP FJR RS BS PS
28-APR-92	TEL		V-14	FDA STATED THAT NO END OF PHASE II MEETING, DATE HAS BEEN SET YET. STEVE MCCORT INFORMED SWPRD THAT HE WILL BE ON A 4 MONTH TEMPORARY DETAIL TO ANOTHER DIVISION EFFECTIVE 04-MAY-92 WHICH MAY BECOME PERMANENT. SUSAN LANGE OR SUSAN KRUMMER WILL BE THE TEMPORARY CSO. CC: PROJECT TEAM DB PC EHC JFF MMK NDL PM OWW CP FJR RS BS PS
30-APR-92	OFC		V-14	FDA CONTACTED RE: THE FOLLOWING; SUMMARY: . WILL ARRANGE DATE FOR END OF PHASE II MEETING. . MR. MCCORT WILL BE ON TEMPORARY DETAIL IN ANOTHER DIVISION. MS. KUMMERER WILL BE OUR NEW CSO; MS. LANGE THE BACKUP. CC: PROJECT TEAM DB PC EHC JFF MMK NDL PM OWW CMP FJR RS BS PS JHD
01-MAY-92	TEL		V-14	FDA SCHEDULED THE END OF PHASE II MEETING, FOR 09-JUN-92 FROM 1:00-2:00 P.M. IN THE MEDICAL IMAGING CONFERENCE ROOM. CC: PROJECT TEAM DB PC EHC JFF MMK NDL PM OWW CMP FJR RS BS PS JHD SA(NYCOMED) PE(SOUS) RJ(S/W)
18-MAY-92	TEL		V-14	FDA IS STILL TRYING TO SCHEDULE END OF, PHASE II MEETING IN JULY. CC: PROJECT TEAM DB PC EHC JFF HH MMK NDL PM OWW FJR RS BS PS
27-MAY-92	SUB	024	V-14	FDA NOTIFIED OF CHANGE IN MEDICAL MONITOR, DR. NORMAN LAFRANCE WILL REPLACE DRS. KITT AND PARADISE AS THE PERSON RESPONSIBLE FOR MONITORING THE CONDUCT AND PROGRESS OF THE CLINICAL INVESTIGATIONS UNDER THE SUBJECT IND. CC: PROJECT TEAM (SA(NYCOMED)) DB JFF HH MK NL OWW+ FJR

IND LOG

WIN Number: 59010
Common Drug Name: TESLASCAN
IND Number: 33031
IND Description: MRI - LIVER LESIONS -INJ

Date(s): (01-JAN-55 -> 01-JAN-99)
Subject: (%)
Communication Type: (%)

Date	Comm.Type	Serial No.	Location	Abstract
11-JUN-92	TEL		V-14	SWPRD DISCUSSED PRE-IND MEETING PHILOSOPHY, SUMMARY: . PRE-IND MEETINGS ARE BEING SUGGESTED BASED UPON POTENTIAL REORGANIZATION OF THE DIVISION AND POSSIBLY A NEW DIVISION DIRECTOR. . "AS AN AGENCY", FDA PERSONNEL ARE BEING ASKED TO RECOMMEND PRE-IND MEETINGS TO ALL COMPANIES FOR ALL PRODUCTS. CC: PROJECT TEAM DM ERC JHD JFF HH DJ MMK NDL TM OWW JAO FR
11-JUN-92	TEL		V-14	END OF PHASE II MEETING IS SCHEDULED FOR, 29-JUN-92 AT 9:30 A.M. IN CONFERENCE ROOM 17B45. CC: DMB PROJECT TEAM FB EC EHC JD JFF HH DJ MK LK NL TM OWW JO FJR
13-JUL-92	TEL		V-15	FDA CONFIRMED CURRENT CHEMISTRY REVIEWER, IS DR. SALAZAR. THE CURRENT MEDICAL REVIEWER IS DR. CHOW. DR. DEWITT, SUPERVISORY PHARMACOLOGIST, HAS NOT ASSIGNED A NEW REVIEWER TO DATE. SWPRD REQUESTED AN OVERHEAD PROJECTOR FOR THE 29-JUL-92 MEETING AND INFORMED FDA THAT THE PRE-MEETING PACKAGE IS TARGETED FOR SUBMISSION ON 15-JUL-92. CC: PROJECT TEAM SA(NYCOMED) DMB EC EHC JD JFF HH DJ MK NL TM OWW JO FJR PE(SOUS) RJ(S/W)
15-JUL-92	OTH		V-15	STAMPED FDA RECEIPT OF SUBMISSION FOR, SERIAL NUMBER 025, THE END OF PHASE II MEETING MATERIALS.
15-JUL-92	SUB	025	V-15	GC: SUBMITTED END OF PHASE II MEETING, MATERIALS WHICH INCLUDED A TABLE OF CONTENTS, SWPRD ATTENDEES, AGENDA, CMC FORMULATION DEVELOPMENT, TOXICOLOGY SUMMARY, AND CLINICAL DATA. CC: PROJECT TEAM (PH+ JR+ TG+ JB+ GD+ PM+) SA(NYCOMED) DMB FB EC EHC JD JFF HH+ DJ MK NL+ TM+ OWW+ JO FJR PE(SOUS) RJ(S/W)
20-JUL-92	TEL		V-15	DR. CHOW CALLED RE: HIS REVIEW OF THE END OF, PHASE II DOCUMENTS. HE QUESTIONED THE USE OF CT IN THE PHASE III PROTOCOL AND QUESTIONED THE LABEL CLAIM IN RELATION TO DISEASE SPECIFICITY. CC: PROJECT TEAM DB EC GC JD JFF HH DJ MK NL TM OWW JO FJR SA(NYCOMED)

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22-JUL-92	TEL		V-15	SUBSEQUENT TO THE INTERNAL FDA MEETING, ON THE END OF PH II MEETING PACKAGE, DR. CHOW RESCINDED ALL COMMENTS MADE IN HIS 20-JUL-92 TELEPHONE CALL ABOUT THE PHASE III PROTOCOL DESIGN AS HIS COLLEAGUES APPEAR TO ACCEPT IT. HE REQUESTED THAT NO REFERENCE BE MADE TO HIS PHONE CALL OR COMMENTS AT THE 29-JUL-92 MEETING. CC: PROJECT TEAM DB EC GC JD JFF HH DJ MK NL TM OWW JO FJR SA(NYCOMED)
27-JUL-92	SUB	026	V-16	INFO.AMEND: PHARM/TOX INCLUDES 3 TOX, REPORTS. CC: PROJECT TEAM (TG+) SA+(NYCOMED) EMB EHC EC JD JFF HH DJ MMK NL TM OWW+ JO FJR
30-JUL-92	OFC		V-16	INFORMAL CONVERSATION WITH DR. CHAMBERS, TO CLARIFY THE COMMENTS MADE AT THE WIN 59010 END OF PHASE II MEETING HELD 29-JUL-92 WHERE THE RANDOMIZATION OF A CLINICAL PROTOCOL/DATABASE INTO TWO WELL CONTROLLED STUDIES WAS DISCUSSED. ASKED DR. CHAMBERS IF THE AGENCY WOULD STILL REQUIRE ADDITIONAL REPRODUCIBILITY STUDIES AFTER THE TWO WELL CONTROLLED STUDIES WERE PERFORMED. DR. CHAMBERS RESPONDED THAT IF TWO OR MORE WELL CONTROLLED STUDIES WERE PERFORMED, REPRODUCIBILITY STUDIES WOULD NOT BE NECESSARY. CC: PROJECT TEAM SA(NYCOMED) DMB EC EHC JD JFF HH DJ MK NL TM OWW JO FR
05-AUG-92	SUB	027	V-16	SUBMITTED COPIES OF SWPRD OVERHEADS, USED AT 29-JUL-92 END OF PHASE II MEETING. CC: DB EC GC JD JFF HH DJ MK NL TM OWW JO FJR SA(NYCOMED) PE(SOUS) RJ(S/W)
07-AUG-92	TEL		V-16	SWPRD NOTIFIED THE FDA THAT THE ANNUAL, REPORT SUBMISSION WILL BE LATE. CC: PROJECT TEAM SA(NYCOMED) EMB EC EHC JD JFF HH DJ MK NL TM OWW JO FJR
19-AUG-92	SUB	028	V-16	ANNUAL REPORT: 05-APR-91 TO 04-APR-92. CC: PROJECT TEAM (PH+ JR+ TM+ FS+ RL+ TG+ JB+ KL+ GD/MD+) SA+(NYCOMED) EMB EC EHC JD JFF HH DJ MK NL TM OWW+ JO FJR
20-AUG-92	SUB	029	V-16	GC: SUBMITTED SWPRD'S MINUTES OF THE, 29-JUL-92 END OF PHASE II MEETING. CC: PROJECT TEAM+

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20-AUG-92	SUB	029	V-16	SA+(NYCOMED) DMB+ EC+ EHC+ JD+ JFF+ HH+ DJ+ MK+ NL+ TM+ OWW+ JO+ FJR+ RS+ PE(SOUS) RJ(S/W)
10-SEP-92	TEL		V-16	INFORMED FDA THAT SWPRD WANTED TO, DISCUSS STATISTICAL METHODOLOGY WITH THE BIOSTATISTICIAN IN CONJUNCTION WITH THE PHASE III PROTOCOL CURRENTLY BEING REVISED. MS. KUMMERER SUGGESTED SUBMITTING THE BIOSTATISTICS PROPOSAL IN WRITING AND THEN SHE WILL DISCUSS IT WITH APPROPRIATE PERSONEL FOR DISPOSITION. NO STATISTICIAN IS OFFICALLY ASSIGNED TO THE IND. SWPRD CONFIRMED THAT PHASE III CLINICAL STUDIES HAVE NOT BEEN STARTED. CC: PROJECT TEAM DB EC EHC JD JFF HH DJ MK NML TM OWW JO FJR
14-OCT-92	TEL		V-16	FDA ACKNOWLEDGED RECEIPT OF STERLING'S END, OF PHASE II MEETING MINUTES OF 29-JUL-92. THEY ARE BEING CIRCULATED FOR REVIEW AND COMMENT; AND WILL SERVE AS JOINT FDA/STERLING MINUTES OF MEETING. CC: PROJECT TEAM DB EC EHC SA(NYCOMED) JFF JJ DJ NL TM OWW JO FR PE(SOUS) RJ(S/W)
22-OCT-92	SUB	030	V-16	SWPRD INFORMED FDA OF ADDRESS CHANGE. CC: PROJECT TEAM SA(NYCOMED) DB EC EHC JD JFF HH DJ NL TM OWW JO FR
22-MAR-93	TEL		V-16	DRA CONTACTED FDA TO DISCUSS THE FOLLOWING, . AWAITING CONFIRMATION THAT STERLING'S AUGUST 20, 1992 END OF PHASE II MEETING MINUTES WILL SERVE AS THE FDA/STERLING JOINT MEETING MINUTES. . MR. ROY BLAY IS NOW THE CSO. CC: PROJECT TEAM DB EC EHC GD JFF HH DJ NL TM OWW JO FR SA(NYCOMED) PE(SOUS) RJ(S/W)
05-APR-93	SUB	031	V-17	INFO.AMEND: PHARM/TOX CONSISTS OF FIVE, TOXICOLOGY REPORTS AND ONE DRUG DISPOSITION REPORT. REPORTS (NOS. 91-015, 91-016, AND 91-017) REPRESENT ADDITIONAL STUDIES CONDUCTED SPECIFICALLY IN SUPPORT OF THE OPTIMIZED FORMULATION OF WIN 59010-2 INJECTION SUBMITTED 05-APR-93. REMAINING REPORTS HAVE JUST BEEN FINALIZED. CC: PROJECT TEAM TG+ JB+ SA+(NYCOMED) DB EC EHC GD JFF HH DJ NL TM DWM JO FR

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Date	Comm.Type	Serial No.	Location	Abstract
05-APR-93	SUB	031	V-17	PE(SOUS) RJ(S/W)
05-APR-93	SUB	032	V-18	INFO.AMEND: CMC PROVIDES FOR DATA TO SUPPORT, AN OPTIMIZED FORMULATION OF WIN 59010-2 INJECTION WHICH WILL BE USED IN PHASE III CLINICAL STUDIES. CC: PROJECT TEAM EC+ RL+ GD+ SA+(NYCOMED) DB EC EHC GD JFF HH DJ NL TM DWM JO FR
06-APR-93	TEL		V-19	FDA CONFIRMED THAT STERLING'S AUG 20, 1992, END OF PHASE II MEETING MINUTES WILL SERVE AS JOINT FDA/STERLING MINUTES. CC: PROJECT TEAM SA(NYCOMED) DB EC EHC GD JFF HH DJ NL TM DWM JO FR PE(SOUS) RJ(S/W)
16-APR-93	SUB	033	V-20	INFO. AMEND: PHARM/TOX, SUBMITTED 6, TOXICOLOGY REPORTS. CC: PROJECT TEAM (TG+ TK+) DMB EC EHC SA+(NYCOMED) GD JFF HH DJ NL TM JO FJR
28-APR-93	SUB	034	V.21-26	INFO.AMEND: CLINICAL INCLUDES TWO FINAL, STUDY REPORTS. CC: PROJECT TEAM TM+ SA+(NYCOMED) DB EC EHC GD JFF HH DJ NL JO FR OWW+
07-MAY-93	SUB	035	V-27	INFO.AMEND: PHARM/TOX PROVIDES A POSITION, PAPER ENTITLED "RATIONALE FOR THE ADEQUACY OF EXISTING BRIDGING STUDIES TO SUPPORT THE OPTIMIZED (50MM) FORMULATION OF WIN 59010-2 INJECTION". CC: PROJECT TEAM OWW+ PH+ TG+ DB SA+(NYCOMED) EC EHC GD JFF HH DJ NL TM+ JO FR
11-MAY-93	SUB	036	V-27	INFO.AMEND: CLINICAL SUBMITTED A REVISED, CLINICAL INVESTIGATOR BROCHURE AND 5 REPLACEMENT PAGES FOR THE PHASE II STUDY REPORT NO. 293 WHICH WAS SUBMITTED ON 28-APR-93 IN SERIAL NO. 034. CC: PROJECT TEAM OWW+ TM+ DB SA+(NYCOMED) EC EHC GD JFF HH DJ NL JO FR PE(SOUS) RJ(S/W)
12-MAY-93	SUB	037	V-27	NP/NI: DR. FEDERLE FOR PROTOCOL 59010-2-001, AND CASE REPORT FORMS FOR PROTOCOL 59010-2-001. CC: PROJECT TEAM OWW+ TM+ LC+ SA+(NYCOMED) DB EHC EC GD JFF HH DJ NL JO FR
14-MAY-93	SUB	038	V-28	NP/NI: DR. MITCHELL FOR PROTOCOL 59010-2-002,

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Date	Comm.Type	Serial No.	Location	Abstract
14-MAY-93	SUB	038	V-28	SUBMITTED CASE REPORT FORMS FOR PROTOCOL 59010-2-002. CC: PROJECT TEAM OWW+ TM+ LC+ SA+(NYCOMED) DB EC EHC GD JFF JFF HH DJ NL TM JO FR
19-MAY-93	TEL		V-29	FDA CONFIRMED THAT THE REVIEWERS HAVE NOT, YET FORMULATED ANY QUESTIONS ON THE WIN 59010-2 TOXICOLOGY BRIDGING STUDIES POSITION PAPER (SERIAL NO. 035) AND THE 001 (SERIAL NO. 037) AND 002 (SERIAL NO. 038) PROTOCOLS. CC: PROJECT TEAM OWW+ SA(NYCOMED) DB EC EHC GD JFF HH DJ NL TM JO FR
19-MAY-93	TEL		V-29	DRA CONTACTED DR. ROY BLAY TO DETERMINE, IF THE REVIEWERS HAD REVIEWED AND COMMENTED ON THE POSITION PAPER AND PROTOCOL 001 AND 002. DR. BLAY INFORMED DRA THAT HE IS NOT AWARE OF ANY FEEDBACK FROM REVIEWERS CONCERNING THE TOXICOLOGY BRIDGING STUDIES POSITION PAPER OR THE CLINICAL 001 AND 002 PROTOCOLS. CC: PROJECT TEAM OWW+ DB EC EHC SA(NYCOMED) GD JFF HH DJ NL TM JO FR
21-MAY-93	TEL		V-29	FDA CONTACTED DRA TO DISCUSSED THE, FOLLOWING: . FDA PROVIDED FEEDBACK AND OBTAINED CLARIFICATION ON SPECIFIC ASPECTS OF THE 59010-2-001 CLINICAL STUDY PROTOCOL. . DR. CHOW WAS CONFUSED ABOUT WHEN BLOOD WOULD BE DRAWN IN RELATIONSHIP TO THE CECT PORTION OF THE PROTOCOL AND ABOUT THE LENGTH OF TIME BETWEEN THE CECT EXAM AND THE MRI EXAM. . DR. CHOW CONFIRMED THAT PATIENTS WOULD BE THOSE WITH KNOWN OR SUSPECTED LIVER LESIONS. . DR. CHOW FELT THE SCATTER PLOTS WERE NOT NECESSARY IF THE LAB PARAMETERS WERE CALCULATED USING 40% OF REFERENCE RANGE. . THE PHASE III STUDY DESIGN FOR THE 001 AND 002 PROTOCOLS IS ACCEPTABLE IN DR. CHOW'S OPINION. . DR. CHOW WILL RECOMMEND TO DR. JONES THAT PHASE III STUDY PROTOCOLS ARE SATISFACTORY AND STUDIES CAN PROCEED, HOWEVER, SWPRD SHOULD TELEPHONE THE AGENCY FOR

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21-MAY-93	TEL		V-29	CONFIRMATION PRIOR TO INITIATING THE STUDIES. CC: PROJECT TEAM OWW SA(NYCOMED) DB EC EHC GD JFF HH DJ NL TM JO FR
27-MAY-93	OTH		V-29	FDA STATED SWPRD SHOULD EXPECT TO RECEIVE, ADDITIONAL COMMENTS FROM FDA ON THE PHASE III 001 AND 002 PROTOCOLS. CC: PROJECT TEAM OWW SA(NYCOMED) DB EC EHC GD JFF HH DJ NL TM JO FR
03-JUN-93	TEL		V-29	AS A FOLLOW-UP TO THE MAY 19TH TELEPHONE, CALL WITH DR. BLAY, DRA INQUIRED IF DR. CHOW AND DR. JONES HAD FINISHED THEIR REVIEW OF THE WIN 59010-2 INJECTION PHASE III PROTOCOLS AND IF THEY HAD ANY SIGNIFICANT COMMENTS. DR. BLAY WAS NOT AWARE OF ANY COMMENTS ON THE PHASE III PROTOCOLS AT THIS TIME. CC: PROJECT TEAM OWW SA(NYCOMED) DB EC EHC GD JFF HH DJ NL TM JO FR
07-JUN-93	TEL		V-29	FDA PROVIDED COMMENTS & RECOMMENDATIONS FOR, PROTOCOLS 59010-2-001 AND 59010-2-002: . DR. JONES INDICATED THAT THE FINAL DIAGNOSIS MUST EXCLUDE THE RESULTS OF THE ENHANCED MRI. IN ADDITION, HE WOULD PREFER THAT UNENHANCED MRI RESULTS ALSO BE EXCLUDED FROM THE FINAL DIAGNOSIS, BUT INDICATED HE WOULD LEAVE THAT DECISION TO STERLING. . DR. JONES SUGGESTED THAT STERLING OBTAIN ADDITIONAL BLOOD SAMPLES ON A SMALL NUMBER OF PATIENTS (10-20) FOR SERIAL SERUM IRON EVALUATIONS. . A QUESTION WAS RAISED REGARDING THE INCLUSION OF CECT IN THE FINAL DIAGNOSIS FOR THE CECT/MRI COMPARISON. DR. JONES HAD NO COMMENT AT THIS TIME AND SUGGESTED THAT IF STERLING WANTED TO DISCUSS THIS FURTHER TO PHONE HIM AFTER JUNE 18TH. . DR. JONES INDICATED THAT THE STUDY COULD BE INITIATED PRIOR TO THE SUBMISSION OF ANY AMENDMENTS AS THE CHANGES DICUSSED DID NOT AFFECT THE CONDUCT OF THE STUDY. . DR. BLAY DID NOT HAVE ANY INFORMATION/COMMENTS ON THE TOXICOLOGY BRIDGING STUDIES PAPER. HE WILL SPEAK WITH THE PHARMACOLOGIST AND CALL SWPRD BACK.

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07-JUN-93	TEL		V-29	CC: PROJECT TEAM OWW SA(NYCOMED) DB EC EHC GD JFF HH DJ NL TM JO FR
28-JUN-93	FAC		V-29	FDA FAXED COMMENTS AND QUESTIONS CONCERNING, THE COMPARISON OF THE S-095 AND WIN 59010-2 FORMULATIONS OF MANGANESE DIPYRIDOXAL DIPHOSPHATE. IN PARTICULAR, INDICATE FOR EACH FORMULATION: . THE MAXIMUM PERMISSIBLE CONCENTRATION OF FREE (NON-CHELATED) MN ION. . THE MAXIMUM PERMISSIBLE CONCENTRATION OF FREE DIPYRIDOXAL DIPHOSPHATE (NOT COMPLEXED WITH MN ION.) . AS ACCURATELY AS POSSIBLE, THE NAME, STRUCTURE, AND CONCENTRATION OF EACH IMPURITY. CC: PROJECT TEAM OWW SA(NYCOMED) DB EC EHC GD JFF HH DJ NL TM JO FR PE(SOUS) RJ(S/W)
01-JUL-93	TEL		V-29	FDA WAS CALLED TO VERIFY THAT THEY, RECEIVED THE FAX DATED 28-JUN-93 WHICH ASKED SWPRD TO PROVIDE ANSWERS TO CHEMISTRY RELATED QUESTIONS. THE ANSWERS TO THESE QUESTIONS WERE REQUESTED TO HELP THE FDA EVALUATE SWPRD'S TOXICOLOGY PAPER ENTITLED "ADEQUACY OF EXISTING BRIDGING STUDIES TO SUPPORT THE OPTIMIZED (50MM) FORMULATION OF WIN 59010-2 INJECTION". CC: PROJECT TEAM DMB EC EHC GD JFF HH DJ NL TM JO FJR JS OWW SA(NYCOMED) PE(SOUS) RJ(S/W)
07-JUL-93	SUB	039	V-29	ANNUAL REPORT FOR THE PERIOD FROM, 05-APRIL-92 TO 04-APR-93. CC: PROJECT TEAM (PH+ TM+ EC+ RL+ TG+ JB+ GD+ MK+ KL+ SA+(NYCOMED)) DMB EC EHC GD JFF HH DJ NL TM JO FJR RS JS OWW+
19-JUL-93	SUB	040	V-29	INFO.AMEND: CMC/MICROBIOLOGY, DRA SUBMITTED, THE FOLLOWING: . POSITION PAPER ENTITLED "JUSTIFICATION FOR THE ASEPTIC PROCESSING OF WIN 59010-2 INJECTION". . COPIES OF CMC DATA FROM END OF PHASE II PRE-MEETING PACKAGE (SUBMITTED JULY 15, 1992, SERIAL NO. 025) AND COPIES OF CMC MEETING OVERHEADS (SUBMITTED AUGUST 5,1992,

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19-JUL-93	SUB	040	V-29	SERIAL NO. 027) CC: PROJECT TEAM OWW+ PH+ EC+ GD+ DF+ SA+(NYCOMED) DB EC EHC GD JFF HH DJ NL TM+ JO FR RS JS WA+ CMD+ WH+ RM+ FS+ PE(SOUS) RJ(S/W)
26-JUL-93	TEL		V-29	DRA CONTACTED FDA TO SUGGEST POSSIBLE DATES, JULY 29TH, 30TH OR AUG 2 FOR THE TELEPHONE CONFERENCE CALL WITH DRS. COONEY AND SALAZAR REGARDING THE ASEPTIC FILL POSITION PAPER. DR. BLAY WILL CONTACT DRS. COONEY AND SALAZAR TO DETERMINE IF THEY HAVE QUESTION ON THE POSITION PAPER AND ARE AVAILABLE FOR A CONFERENCE CALL ON ONE OF THE PROPOSED DATES. FDA STATED SUBMISSION OF A DISKETTE, IN ADDITION TO THE HARDCOPY, FOR THE JUNE 28TH RESPONSE TO FDA REQUEST FOR INFORMATION WOULD BE HELPFUL. CC: PROJECT TEAM OWW SA(NYCOMED) DB EC EHC GD JFF HH DJ NL TM JO FR RS JS SA(NYCOMED) RJ(S/W) PE(SOUS)
26-JUL-93	TEL		V-29	FDA CALLED DRA TO DISCUSS THE FOLLOWING:, . AT THIS TIME, DR. COONEY HAS NO QUESTIONS REGARDING THE ASEPTIC FILL POSITION PAPER (SUBMITTED JULY 19, 1993; SERIAL NO. 040) BUT IT WAS NOT CONFIRMED HE'D THOROUGHLY REVIEWED IT. . DR. COONEY IS NOT AVAILABLE UNTIL AUGUST 9TH FOR A TELEPHONE CONFERENCE CALL ON THE ASEPTIC FILL POSITION PAPER. . DR. BLAY WAS UNABLE TO CONTACT DR. SALAZAR TO DETERMINE HER AVAILABILITY FOR A TELEPHONE CONFERENCE CALL THIS WEEK. . SUBMISSION OF A DISKETTE FOR THE JUNE 28TH RESPONSE TO INFORMATION REQUEST WOULD BE WELCOME. CC: PROJECT TEAM OWW SA(NYCOMED) DB EC EHC GD JFF HH DJ NL TM JO FR RS JS PE(SOUS) RJ(S/W)
29-JUL-93	TEL		V-29	FDA RETURNED DRA'S TELEPHONE CALL TO, FOLLOW-UP JULY 26, 1993 DISCUSSION. DR. BLAY INFORMED DRA THAT HE WILL SEND A MESSAGE TO DRS. COONEY AND SALAZAR INDICATING STERLING IS REQUESTING THEIR INPUT ON THE "JUSTIFICATION FOR THE ASEPTIC PROCESSING OF WIN 59010-2

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29-JUL-93	TEL		V-29	INJECTION" POSITION PAPER. DR. BLAY WILL CONTACT DRA AS SOON AS HE RECEIVES THEIR RESPONSES. CC: PROJECT TEAM SA(NYCOMED) DB EC EHC GD JFF HH DJ NL TM JO FR RS JS OWW PE(SOUS) RJ(S/W)
06-AUG-93	TEL		V-29	DRA CONTACTED FDA REGARDING JUNE 7, 1993, TELEPHONE CONFERENCE CALL DURING WHICH WIN 59010-02-001 AND 002 CLINICAL PROTOCOLS WERE DISCUSSED. FDA REQUESTED THAT STERLING PREPARE A BRIEF AND CONCISE STATEMENT WHICH IDENTIFIES THE STRATEGY AND RATIONALE TO ADDRESS DR. JONES' JUNE 7TH COMMENT REGARDING THE COLLECTION OF SERIAL SERUM IRON SAMPLES. THIS INFORMATION SHOULD BE SUBMITTED TO FDA DURING THE WEEK OF AUGUST 9TH FOR DR. JONES TO REVIEW. DRA INQUIRED AS TO THE MOST CONVENIENT WAY TO PROVIDE THE DISKETTE TO DR. SEE. FDA STATED ONLY ONE DISKETTE NEEDS TO BE SUBMITTED. CC: PROJECT TEAM SA(NYCOMED) DB EC EHC GD JFF HH DJ TM JO RR FR RS OWW PE(SOUS) RJ(S/W)
10-AUG-93	SUB	041	V-29	INFO.AMEND: PHARM/TOX, DRA SUBMITTED TWO, FINAL REPORTS BY DAIICHI PHARMACEUTICAL CO., LTD., TOKYO, JAPAN AND ARE PERTINENT TO THE SAFETY ASSESSMENT OF WIN 59010-2 INJECTION. CC: PROJECT TEAM OWW+ TG+ SA+(NYCOMED) DB EC EHC GD JFF HH DJ TM JO RR FR RS
11-AUG-93	TEL		V-29	FDA INFORMED DRA THAT DR. JONES WILL BE, IN THE OFFICE DURING THE WEEK OF AUGUST 16. ON AUGUST 13TH DR. BLAY WILL PROVIDE AN UDATE ON DRS. COONEY AND SALAZAR'S PROGRESS ON REVIEWING THE POSITION PAPER ENTITLED "JUSTIFICATION FOR THE ASEPTIC PROCESSING OF WIN 59010-2 INJECTION", SUBMITTED JULY 19, 1993; SERIAL NO. 040. CC: PROJECT TEAM SA(NYCOMED) OWW DB EC EHC GD JFF HH DJ JO RR FR RS PE(SOUS) RJ(S/W)
11-AUG-93	TEL		V-29	DR. BLAY INFORMED DRA THAT HE WILL REMIND, DRS. COONEY AND SALAZAR THAT STERLING IS REQUESTING THEIR INPUT ON THE POSITION PAPER ENTITLED "JUSTIFICATION FOR THE ASEPTIC PROCESSING OF WIN 59010-2 INJECTION", SUBMITTED JULY 19, 1993; SERIAL NO.040. DR. BLAY WILL CHECK DR. JONES'

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Date	Comm.Type	Serial No.	Location	Abstract
11-AUG-93	TEL		V-29	CALENDAR FOR AVAILABILITY DURING THE NEXT TWO WEEK TO DISCUSS STERLING'S PLAN TO COLLECT SERIAL IRON SAMPLES. CC: PROJECT TEAM SA(NYCOMED) OWW DB EC EHC GD JFF HH DJ JO RR FR RS PE(SOUS) RJ(S/W)
16-AUG-93	SUB	042	V-29	RESPONSE TO FDA INFORMATION REQUEST OF, 28-JUN-93. DRA PROVIDED COMPLETE RESPONSE TO THE CMC QUESTIONS DR. SEE HAD AS A RESULT OF HIS REVIEW OF THE POSITION PAPER ENTITLED "RATIONALE FOR THE ADEQUACY OF EXISTING BRIDGING STUDIES TO SUPPORT THE OPTIMIZED FORMULATION OF WIN 59010-2 INJECTION. DRA IS PROVIDING DR. SEE WITH A DESK COPY OF THIS SUBMISSION AS WELL AS A COPY OF IT ON DISKETTE IN WORD PERFECT 5.1 FORMAT. CC: PROJECT TEAM OWW+ EC+(WITH DISK) RL+ TG+ BH+ DB EC EHC SA+(NYCOMED) GD JFF HH DJ JO RR FR RS PE(SOUS) RJ(S/W)
16-AUG-93	SUB	043	V-29	GC: INFORMED FDA THAT DR. RONALD ROBISON, REPLACES NORMAN LAFRANCE AS MEDICAL MONITOR. CC: PROJECT TEAM OWW+ TM+ SA+(NYCOMED) DB EC EHC GD JFF HH DJ JO RR FR RS
17-AUG-93	TEL		V-29	FDA INFORMED DRA THAT, . DRS. COONEY AND SALAZAR HAVE COMPLETED THEIR REVIEW OF THE POSITION PAPER ENTITLED "JUSTIFICATION FOR THE ASEPTIC PROCESSING OF WIN 59010-2 INJECTION" (SUBMITTED 19-JUL-93, SERIAL NO. 040), AND ARE READY TO SCHEDULE A TELEPHONE CONFERENCE TO DISCUSS THEIR QUESTIONS. . THE TELEPHONE CONFERENCE CALL TO DISCUSS THE ASEPTIC FILL POSITION PAPER IS SCHEDULED FOR 18-AUG-93 AT 2:00 PM. . STERLING'S PROPOSAL TO ADDRESS DR. JONES' 07-JUN-93 COMMENT REGARDING SERIAL SERUM IRON SAMPLING IS STILL IN PROGRESS. CC: PROJECT TEAM OWW DB EC EHC GD JFF HH DJ JO RR CMD RM GM FS SA(NYCOMED) FR RS WA PE(SOUS) RJ(S/W)
18-AUG-93	TEL		V-29	FDA CANCELED THE 18-AUG-93 TELEPHONE, CONFERENCE CALL AND RESCHEDULED IT FOR 19-AUG-93. DRS. COONEY AND SALAZAR WILL BE ASKING QUESTIONS REGARDING THE

IND LOG

WIN Number: 59010
Common Drug Name: TESLASCAN
IND Number: 33031
IND Description: MRI - LIVER LESIONS -INJ

Date(s): (01-JAN-55 -> 01-JAN-99)
Subject: (%)
Communication Type: (%)

Date	Comm.Type	Serial No.	Location	Abstract
18-AUG-93	TEL		V-29	POSITION PAPER ENTITLED, "JUSTIFICATION FOR THE ASEPTIC PROCESSING OF WIN 59010-2 INJECTION". CC: PROJECT TEAM OWW DB EHC EC GD JFF HH DJ JO RR FR RS WA CMD RM GM FS SA(NYCOMED) PE(SOUS) RJ(S/W)
19-AUG-93	TEL		V-29	FDA AND SWPRD HELD A TELEPHONE CONFERENCE, CALL TO ANSWER QUESTIONS RAISED BY DRS. COONEY AND SALAZAR REGARDING STERLING'S POSITION PAPER TITLED " JUSTIFICATION FOR THE ASEPTIC PROCESSING OF WIN 59010-2 INJECTION" WHICH WAS SUBMITTED 19-JUL-93; SERIAL NO. 040. STERLING'S OBJECTIVE IN SUBMITTING THE PAPER WAS TO OBTAIN FDA CONCURRENCE THAT ASEPTIC FILLING WAS APPROPRIATE FOR WIN 59010-2 INJECTION AND THE NDA MICROBIOLOGICAL PLAN PROPOSED WAS ACCEPTABLE. FDA STATED THERE WERE NO REGULATIONS IN EFFECT REQUIRING TERMINAL STERILIZATION. A FALL FORUM IS PLANNED FOR THIS TOPIC. CC: PROJECT TEAM OWW SA(NYCOMED) EC GD JFF HH DJ JO RR FR RS WA GM(ALNWICK) FS RJ(SW-KS) PE(SOUS-NY)
26-AUG-93	TEL		V-29	FDA REQUESTED A DESK COPY, OF THE IND PRECLINICAL SECTIONS THAT WERE SUBMITTED IN THE ORIGINAL IND. ROY BLAY CALLED BACK ON 27-AUG-93 TO CANCEL THE REQUEST; FDA LOCATED THE MISPLACED COPY. CC: PROJECT TEAM OWW DB EC GD JFF HH DJ JO RR FR RS WA GM FS SA(NYCOMED)
27-AUG-93	TEL		V-29	FDA INFORMED DRA THAT, . FDA OPEN MEETING ON ASEPTIC VERSUS TERMINAL STERILIZATION TO BE HELD 12/13-OCT-93. . FDA IS PREPARING MINUTES FOR THE TELEPHONE CONFERENCE CALL HELD 19-AUG-93. CC: PROJECT TEAM OWW DB EC GD JFF HH DJ JO RR FR RS WA GM FS SA(NYCOMED) PE(SOUS) RJ(S/W)
16-SEP-93	TEL		V-29	FDA REQUESTED A DESK COPY OF THE PRECLINICAL, SECTION FOR IND 33,031 (VOL. 2-5; 4-APRIL-89, SERIAL NO.

IND LOG

WIN Number: 59010
Common Drug Name: TESLASCAN
IND Number: 33031
IND Description: MRI - LIVER LESIONS -INJ

Date(s): (01-JAN-55 -> 01-JAN-99)
Subject: (%)
Communication Type: (%)

Date	Comm.Type	Serial No.	Location	Abstract
16-SEP-93	TEL		V-29	000). . FDA ASKED STERLING TO PRIORITIZE DR. SEE'S WORKLOAD FOR IND 33,031 (WIN 59010-2 INJECTION) AND IND 41,200 (WIN 39996) AND PROVIDE TARGET DATES FOR SUBMISSION OF THE NDAS. . DR. SALAZAR WOULD WELCOME A COPY OF THE WIN 59010-2 INJECTION CMC AMENDMENT ON DISKETTE. CC: PROJECT TEAM OWW EC GD JFF HH DJ JO RR FR RS SA(NYCOMED)
17-SEP-93	SUB	044	V-29	SWPRD MINUTES OF THE 19-AUG-93 TELEPHONE, CONFERENCE CALL WITH THE FDA TO DISCUSS THE POSITION PAPER TITLED "JUSTIFICATION FOR THE ASEPTIC PROCESSING OF WIN 59010-2 INJECTION". DRA STATED THAT IF THE FDA DOESN'T RESPOND WITHIN 30 DAYS, IT WILL BE ASSUMED THAT THE FDA IS IN AGREEMENT WITH THE CONCLUSIONS. CC: PROJECT TEAM OWW+ PH+ PS+ TM+ EC+ RL+ TG+ JB+ WH+ TM+ DF+ TK+ ED+ SA+(NYCOMED) EC GD JFF HH DJ JO RR FR RS WA+ GM+ FS+ RJ+ PE+
17-SEP-93	TEL		V-29	DRA RESPONDED TO FDA'S REQUEST FOR, INFORMATION ON 16-SEPT-93. . SWPRD'S REQUEST FOR THE WAIVER TO PERFORM REPRODUCTIVE TOXICOLOGY STUDIES (IND 41,200; 1-DEC-92, SERIAL NO. 000) SHOULD BE PRIORITIZED FOR DR. SEE OVER THE POSITION PAPER ENTITLED "RATIONALE FOR THE ADEQUACY OF EXISTING BRIDGING STUDIES TO SUPPORT THE OPTIMIZED (50MM) FORMULATION OF WIN 59010-2 INJECTION" (IND 33,031; 7-MAY-93, SERIAL NO. 035). THE NDA FOR BOTH PRODUCTS IS TARGETED FOR 1995. CC: PROJECT TEAM OWW EC GD JFF HH DJ JO RR FR FS SA(NYCOMED)
21-SEP-93	SUB	045	V.30-33	RESPONSE TO FDA INFORMATION REQUEST, DATED 16-SEP-93 FOR PRECLINICAL INFORMATION SUBMITTED BY SALUTAR, INC. IN THE ORIGINAL IND (SERIAL NO. 000) ON 14-APR-89. DRA SUBMITTED VOLUMES 2 THROUGH 5 WHICH ARE IND SECTIONS 8 THROUGH 11. CC: PROJECT TEAM OWW SA(NYCOMED) EC GD JFF HH DJ JO RR FR RS RB
05-OCT-93	SUB	046	V-34	GC/RESPONSE TO FDA INFORMATION REQUEST,

IND LOG

WIN Number: 59010
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IND Number: 33031
IND Description: MRI - LIVER LESIONS -INJ

Date(s): (01-JAN-55 -> 01-JAN-99)
Subject: (%)
Communication Type: (%)

Date	Comm.Type	Serial No.	Location	Abstract
05-OCT-93	SUB	046	V-34	DATED 06-AUG-93. DRA SUBMITTED BACKGROUND INFORMATION AND PROPOSAL ENTITLED" PROPOSAL TO EVALUATE SERUM IRON CHANGES OBSERVED IN WIN 59010-2 PHASE III STUDIES" TO DR. JONES FOR HIS REVIEW. COPIES OF PUBLICATIONS REFERENCED IN THIS PROPOSAL HAVE BEEN INCLUDED. CC: PROJECT TEAM TM+ DF+ LC+ SA+(NYCOMED) EC GD JFF HH DJ JO RR FR RS OWW+
13-OCT-93	TEL		V-34	FDA INQUIRED IF DRA WAS AWARE OF THE, PROBLEMS FDA'S BEEN HAVING WITH THE COMBINED PHASE II/III PROTOCOLS. DRA INFORMED FDA THE COMBINED PHASE II/III PROTOCOL CONCEPT WAS BEING ADDRESSED ACROSS ALL IMAGING AGENTS. FDA RECOMMENDED THE FOLLOWING: . IF FORMATTING COMBINED PHASE II/III PROTOCOL, PRESENT CLEAR, CONCISE DISTINCTION REGARDING THE COMPONENTS OF EACH PHASE. . FOR NEW PROTOCOLS, SPECIFY WHAT IS DIFFERENT FROM THE PREVIOUS ONES SUBMITTED, WHEN APPLICABLE. CC: RA MA PA PC SD JFF DF DF FFR DG LH KK TM MM FR BS DZ OWW
20-OCT-93	TEL		V-34	DRA CALLED TO DETERMINE THE REVIEW STATUS, OF THE SERUM IRON PROPOSAL, MINUTES OF THE JULY 19 TELEPHONE CONFERENCE CALL AND THE TOXICOLOGY BRIDGING STUDY POSITION PAPER. DR. BLAY WILL CHECK ON THE STATUS OF THESE ITEMS AND CALL BACK. CC: PROJECT TEAM SA(NYCOMED) EC GD JFF HH DJ JO RR FR RS PE RJ OWW
02-NOV-93	FAC		V-34	FDA FAXED PHARMACOLOGY COMMENTS REGARDING, SUBMISSIONS 035 AND 042. SWPRD REQUESTED AN FDA OPINION CONCERNING THE USE OF NON-CLINICAL STUDIES CONDUCTED WITH A PREVIOUS FORMULATION OF MANGANESE DYPYRIDOXAL DISPHOSPHATE (S-095) TO SUPPORT THE SAFETY OF THE CURRENT FORMULATION OF THAT AGENT (WIN 59010-2). FDA STATED TO PERMIT COMPARISON OF THE TOXICITY POTENTIALS OF THE TWO FORMULATION, IT WILL BE NECESSARY TO COMPARE THE IMPURITY PROFILES OF THE TWO FORMULATIONS. FDA REQUESTED THAT SWPRD SUBMIT CHEMICAL ANALYSES OF AT LEAST TWO LOTS OF EACH FORMULATION, INCLUDING THE NAME AND CONCENTRATION OF EACH IMPURITY. CC: PROJECT

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Subject: (%)
Communication Type: (%)

Date	Comm.Type	Serial No.	Location	Abstract
02-NOV-93	FAC		V-34	TEAM. CC: PROJECT TEAM
02-NOV-93	TEL		V-34	DRA CONTACTED FDA AS A FOLLOW-UP TO, THE 20-OCT-93 CONTACT. DR. BLAY STATED THAT A LETTER HAS BEEN DRAFTED WHICH RESPONDS TO THE SERIAL SERUM IRON SAMPLING PROPOSAL FOR PHASE III CLINICAL STUDIES (SUBMITTED 05-OCT-93; SERIAL NO. 046). ACCORDING TO DR. BLAY, THE MINUTES FROM THE TELEPHONE CONFERENCE REGARDING ASEPTIC FILL VERSUS TERMINAL STERILIZATION HAVE BEEN APPROVED. DR. BLAY INDICATED THAT HE WOULD BE SENDING COMMENTS/REQUESTS ON THE TOXICOLOGY BRIDGING POSITION PAPER WHICH WAS SUBMITTED 21-SEP-93; SERIAL NO. 045). CC: PROJECT TEAM OWW SA(NYCOMED) EC GD JFF HH DJ JO RR FR RS PE RJ
18-NOV-93	SUB	047	V-35	INFO.AMEND: CMC, DRA PROVIDED DATA TO, TO SUPPORT PHASE III CLINICAL SUPPLIES. THESE SUPPLIES WILL BE USED FOR PROTOCOL 59010-2-001 AND 59010-2-002. DRA PROVIDED INFORMATION CONCERNING THE FOLLOWING UNDER: DRUG SUBSTANCE: . STERLING WINTHROP INC. CHEMICAL GROUP, STERLING ORGANICS, U.S., RENSSELAER, NEW YORK. . NYCOMED AS OSLO, NORWAY. . THE WITHDRAWAL OF SWPRD, RENSSELAER, NY AS MANUFACTURER, PACKAGER, AND DISTRIBUTOR OF CLINICAL DRUG PRODUCT . UPDATED THE CLINICAL LABEL TO PROVIDE FOR ADDRESS CHANGE. DRUG PRODUCT: . ADDITION OF TWO MANUFACTURERS. PACKAGING MAY BE CONDUCTED AT STERLING WINTHROP INC. (SWPRD) COLLEGEVILLE, PA. AND ALMEDICA SERVICES CORP. DRA PROVIDED DR. SALAZAR WITH A DESK COPY AND A 3.5 HIGH DENSITY DISKETTE IN WORDPERFECT 5.1 FORMAT OF THIS SUBMISSION.
18-NOV-93	SUB	048	V.36-37	PC/NI/RESPONSE TO INFORMATION REQUEST, PROTOCOL CHANGES: . 59010-2-001,A-01 AND 59010-2-002,A-01 CONTAINS MODIFICATIONS TO THE TITLE PAGE AND CHANGES TO SECTIONS INVOLVING THE OBJECTIVES, STUDY PLAN/DESIGN,

IND LOG

WIN Number: 59010
Common Drug Name: TESLASCAN
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Date(s): (01-JAN-55 -> 01-JAN-99)
Subject: (%)
Communication Type: (%)

Date	Comm.Type	Serial No.	Location	Abstract
18-NOV-93	SUB	048	V.36-37	TREATMENT PLAN, DIAGNOSIS DEFINITIONS, AND ENDPOINTS. . 59010-2-001,A-02 AND 59010-2-002,A-02 CONTAINS CHANGES TO THE ELIGIBILITY. TREATMENT PLAN, DIAGNOSIS DEFINITIONS, AND ENDPOINTS. DRS. CHEZMAR, FREENY, AND WEINREB FOR PROTOCOLS 59010-2-001, 59010-2-001,A-01 AND 59010-2-001,A-02. DRS. BROWN, HALFORD, HARMS, LEE, MATTREY, RIFKIN, RUBIN, SAINI, AND YOUNG FOR PROTOCOLS 59010-2-002, 59010-2-002,A-01, AND 59010-2-002,A-02.
22-NOV-93	SUB	049	V-38	INFO. AMEND: CMC WHICH PROVIDES DATA, TO SUPPORT PROTOCOL 59010-2-005. THIS DOCUMENTATION IS SPECIFIC TO THE CMC OF THE 14C LABELED DRUG SUBSTANCE AND DRUG PRODUCT. A DESK COPY WAS SENT TO DR. SALAZAR.
22-NOV-93	SUB	050	V-38	NP/PC/NI: DR. IZQUIERDO FOR PROTOCOL, 59010-2-005 AND 59010-2-005,A-01. PROTOCOL 59010-2-005,A-01 PROVIDES THE FOLLOWING CHANGE: . THE SINGLE 10 UMOL/KG INTRAVENOUS DOSE RECEIVED BY EACH SUBJECT HAS BEEN CHANGED TO A SINGLE INTRAVENOUS DOSE OF 5 UMOL/KG.
02-DEC-93	FAC		V-38	FDA'S FAXED COMMENTS REQUESTED THAT THE, SUBMITTED PROPOSAL FOR PHASE III CLINICAL STUDIES (SERIAL NO. 046, DATED 05-OCT-93) BE MODIFIED TO INCLUDE TWO ADDITIONAL BLOOD SAMPLES: PRIOR TO INJECTION AT 8 HOURS (8:00 P.M.) AND POST INJECTION AT +12 HOURS (8:00 P.M.).
02-DEC-93	TEL		V-38	FDA CALLED TO ALERT DRA OF A FAX THAT, WAS SENT REGARDING THE AGENCY'S COMMENT TO SWPRD'S SERUM IRON SAMPLING PROPOSAL FOR PHASE III CLINICAL STUDIES (SERIAL NO. 046, DATED 05-OCT-93).
21-JAN-94	SUB	051	V-38	INFO.AMEND: PHARM/TOX INCLUDES ONE STUDY, REPORT (NO. 1364).
04-FEB-94	TEL		V-38	FDA IS REQUIRING PRE-MEETING SUBMISSION, PACKAGES TO BE SENT 5 WEEKS IN ADVANCE. FDA STATED THE

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Subject: (%)
Communication Type: (%)

Date	Comm.Type	Serial No.	Location	Abstract
04-FEB-94	TEL		V-38	STABILITY REQUIREMENTS IN THE IMAGING DIVISION MAY BE IMPACTED BY RECENT ICH GUIDELINES.
04-FEB-94	TEL		V-38	FDA STATED WHEN MANUFACTURING A STABILITY, BATCH THE ENTIRE BATCH MUST BE FILLED/PACKAGED IN ORDER TO SATISFY THE RANDOMNESS OF THE SAMPLING FOR STABILITY TESTING.
07-FEB-94	SUB	052	V-38	RESPONSE TO INFORMATION REQUEST DATED, 02-NOV-93. DRA SUBMITTED INFORMATION REGARDING THE IMPURITY PROFILES OF THE TWO FORMULATIONS (S-095 AND WIN 59010-2). A DESK COPY AND DISKETTE IN WORDPERFECT 5.2 FORMAT CONTAINING THE RESPONSE TO FDA QUESTIONS WERE SENT TO DR. SEE.
23-FEB-94	SUB	053	V-38	NP/NI: DRA SUBMITTED PROTOCOLS 59010-2-003, AND 59010-2-004. DR. HARMON FOR PROTOCOL 59010-2-003. PAREXEL INTERNATIONAL CORP. WILL PROVIDE SERVICES FOR STUDY INITIATION AND CLINICAL SITE MONITORING, AND PROVIDE DATA MANAGEMENT SERVICES FOR PROTOCOLS 59010-2-003 & 59010-2-004.
28-FEB-94	TEL		V-38	FDA INFORMED DRA THAT SWPRD'S PROPOSAL FOR, SERUM IRON SAMPLING IN NORMAL SUBJECTS IS BEING REVIEWED INFORMALLY BY DR. JONES. IT IS PREFERRABLE TO SEND TO THE FDA PROTOCOLS FOR HOW BLIND READS WILL BE CONDUCTED FOR IMAGING PRODUCTS.
07-MAR-94	SUB	054	V-39	GC: RESPONSE TO FDA REQUEST FOR INFORMATION, DATED 02-DEC-93. DRA SUBMITTED THE PROPOSED PROTOCOL ABSTRACT ENTITLED: WIN 59010-2 INJECTION PHASE I STUDY FOR ASSESSMENT OF EFFECTS ON SERUM IRON.
08-MAR-94	SUB	055	V-39	PC: DRA SUBMITTED PROTOCOL AMENDMENT A-03, FOR PROTOCOLS 59010-2-001 AND 59010-2-002. THESE AMENDMENTS PROVIDE FOR ADDITION INVESTIGATIONAL SITES TO BE RECRUITED TO ENSURE TIMELY ENROLLMENT.
10-MAR-94	SUB	056	V-39	GC: DRA SUBMITTED CORRECTIONS TO CMC,

IND LOG

WIN Number: 59010
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Subject: (%)
Communication Type: (%)

Date	Comm.Type	Serial No.	Location	Abstract
10-MAR-94	SUB	056	V-39	INFORMATION AMENDMENT SUBMITTED 18-NOV-94 (SERIAL NO. 047). THE CORRECTIONS HAVE BEEN MADE TO TABLE 1 PAGE 5.
07-APR-94	SUB	057	V-40	PC/NI: PROTOCOL 59010-2-003,A-01 AND, 59010-2-004,A-01 PROVIDES FOR A CORRECTION IN THE CALCULATION ALGORITHM USED TO GENERATE THE POWER TABLE. THIS CORRECTION ALLOWS FOR ADEQUATE POWER FOR DETECTING A DIFFERENCE OF 15% OR MORE WHILE RETAINING A SAMPLE SIZE OF SIXTY(60). DRS. BENNETT AND DACHMAN FOR PROTOCOL 59010-2-001. DRS. ANDERSON AND GAY FOR PROTOCOL 59010-2-002. DRS. KLIPPENSTEIN AND YUH FOR PROTOCOL 59010-2-003. DRS. FRANCIS AND NELSON FOR PROTOCOL 59010-2-004.
08-APR-94	TEL		V-41	FDA INFORMED DRA THAT THE AGENCY RESPONSE, TO SWPRD'S POSITION REGARDING THE NEED FOR ADDITIONAL TOX BRIDGING STUDIES IS COMING SOON. CONCERNING THE RABBIT TERATOLOGY STUDY, DR. SEE INDICATED THE DIVISION MAY WANT TO SEE A DEFINITIVE RABBIT TERATOLOGY STUDY IN THE NDA.
08-APR-94	TEL		V-41	FDA CALLED TO DETERMINE WHAT DOSAGE WAS, CURRENTLY IN THE PROPOSED LABELLING FOR WIN 59010-2.
13-APR-94	SUB	058	V-41	SAFETY REPORT FOR PROTOCOL 59010-2-001, DR. SCHMIEDL'S PATIENT "TK" (SUBJECT NO. 018) EXPERIENCED SEVERE NAUSEA.
14-APR-94	TEL		V-41	FDA CALLED TO DETERMINE WHAT DOSAGE WAS, CURRENTLY IN THE PROPOSED LABELLING FOR WIN 59010-2. DRA RESPONDED THAT THE ANTICIPATED MAXIMUM DOSE IS 5 UMOL/KG.
25-APR-94	SUB	059	V-41	RESPONSE TO FDA REQUEST FOR INFORMATION, DATED 28-FEB-94. DRA PROVIDED THE BLINDED IMAGE READING PROCEDURES AND THEIR RESPECTIVE CASE REPORT FORMS FOR PROTOCOLS 59010-2-001, 59010-2-002, 59010-2-003, AND 59010-2-004.
03-MAY-94	LPF		V-41	FDA COMPLETED THE INITIAL REVIEW OF SERIAL,

IND LOG

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Date	Comm.Type	Serial No.	Location	Abstract
03-MAY-94	LFF		V-41	NO. 023, DATED 23-FEB-94. FDA PROVIDED COMMENTS AND REQUESTS FOR FURTHER INFORMATION.
10-MAY-94	TEL		V-41	DR. BLAY AGREED TO ARRANGE A CONFERENCE CALL, TO DISCUSS THE LETTER OF 03-MAY-94 REGARDING SERIAL NO. 053. A DESK COPY OF SERIAL NO. 053 WAS SENT TO DR. BLAY.
13-MAY-94	SUB	060	V-42	INFO.AMEND: PHARM/TOX PROVIDES STUDY REPORTS, 1713 AND 1541.
13-MAY-94	SUB	061	V-43	PC/NI: PROTOCOL 59010-2-002,A-04 PROVIDES, FOR THE UPPER LIMIT FOR MAXIMUM ENROLLMENT AT A SINGLE SITE TO INCREASE FROM 30 TO 40 PATIENTS. DR. KENNEY FOR PROTOCOL 59010-2-003. DRS. FENSTERMACHER, JOHNSON, STILLMAN AND TURNER FOR PROTOCOL 59010-2-004.
18-MAY-94	TEL		V-43	FDA AND DRA SCHEDULED CONFERENCE CALL ON, FRIDAY 27-MAY-94 AT 11:00 A.M. TO DISCUSS THE 03-MAY-94 LETTER FROM FDA REGARDING SERIAL NO. 053 (DELAYED IMAGING PROTOCOL).
23-MAY-94	SUB	062	V-43	PC: PROTOCOLS 59010-2-003,A02 AND, 59010-2-004,A-02 PROVIDE FOR AN INCREASE IN THE NUMBER OF CENTERS SPECIFIED IN THE STUDY DESIGN TO ALLOW FASTER ENROLLMENT OF PATIENTS.
26-MAY-94	TEL		V-43	FDA AND DRA AGREED THAT THE TELEPHONE, CONFERENCE CALL TO DISCUSS FDA'S 03-MAY-94 LETTER REGARDING SERIAL NO. 053 (DELAYED IMAGING PROTOCOL) WILL TAKE PLACE ON THURSDAY, 02-JUN-94 AT 2:30.
27-MAY-94	TEL		V-43	DR. BLAY, CSO, INDICATED THAT HE WOULD SEE, IF FDA'S STATISTICIAN WILL BE AVAILABLE FOR THE TELEPHONE CONFERENCE ON JUNE 2. FDA'S RESPONSE TO SWPRD'S PROPOSAL REGARDING TOX BRIDGING STUDIES IS STILL AWAITING MANAGEMENT SIGNOFF. DR. BLAY WILL ASK PERMISSION TO FAX DRA "REFUSE TO FILE" CHECKLIST.

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Date	Comm.Type	Serial No.	Location	Abstract
01-JUN-94	TEL		V-43	FDA CALLED TO CONFIRM THE ISSUES TO BE, DISCUSSED FOR THE TELECONFERENCE ON 02-JUN-94. FDA INFORMED DRA THAT AN FDA STATISTICIAN WILL NOT BE AVAILABLE FOR THE TELECONFERENCE.
02-JUN-94	MOM		V-43	MINUTES OF TELEPHONE CONFERENCE TO CLARIFY, COMMENTS/REQUESTS NUMBERED 4, 5, 7, TO 9 AND 14 FROM THE LETTER DATED 03-MAY-94, WITH COMMENTS ON THE DELAYED IMAGING PROTOCOL 003 AND 004. SUMMARY OF TELEPHONE CONFERENCE AS FOLLOWS: . DR. LOVE WOULD LIKE TO REVIEW THE PHASE I STUDY PROTOCOL 006 (SERUM IRON) AND THE STATISTICAL SUPPORT TO SHOW THAT IT HAS A LARGE ENOUGH SAMPLE SIZE. . STERLING WILL SUBMIT TO THE AGENCY A PROTOCOL AMENDMENT TO PROVIDE 24 HOURS BETWEEN ADMINISTRATION OF IODINATED CONTRAST AGENT AND WIN 59010-2. . STERLING WILL SUBMIT TO THE AGENCY THE MAP OF THE LIVER WHICH WILL BE USED TO CORRELATE THE LESION IMAGED WITH THE BIOPSIED LESION IN THE BLINDED READ. . DR. LOVE WOULD LIKE A PLACEBO STUDY IN THE CLINIC FOR THE PURPOSE OF CHARACTERIZING THE SAFETY PROFILE. STERLING WILL PROVIDE A PLACEBO PROTOCOL FOR AGENCY REVIEW.
10-JUN-94	FAC		V-43	FDA FAXED REVIEWING PHARMACOLOGIST'S, COMMENTS ON IND 33031 AS FOLLOWS: . IN REFERENCE TO AMENDMENTS 035, 042, AND 052, THE NON-CLINICAL STUDIES CONDUCTED WITH THE ORIGINAL (145MM) FORMULATION OF WIN 59010 WILL BE CONSIDERED TO PROVIDE DATA RELEVANT TO THE SAFETY ASSESSMENT OF THE 50 MM FORMULATION OF WIN 59010. . IT IS RECOMMENDED THAT THE IND BE REEVALUATED FOR TERATOGENIC POTENTIAL IN THE RABBIT. THE STUDY SHOULD INCLUDE AT LEAST ONE DOSAGE THAT INDUCES ADEQUATE EVIDENCE OF EITHER MATERNAL OR FETAL TOXICITY. IF TOXICITY IS NOT OBSERVED, THE ADEQUACY OF THE LARGEST DOSAGE USED SHOULD BE JUSTIFIED. JUSTIFICATION COULD BE ACCOMPLISHED THROUGH COMPARISION OF ANIMAL DOSAGE TO THE MAXIMUM PROPOSED CLINICAL DOSAGE FOLLOWING

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Date	Comm.Type	Serial No.	Location	Abstract
10-JUN-94	FAC		V-43	NORMALIZATION OF THE DOSAGES ON THE BASIS OF BODY SURFACE AREA (UMOL/M2) OR THROUGH SUBMISSION OF ADEQUATE TOXICOKINETIC DATA.
14-JUN-94	SUB	063	V-43	INFO.AMEND: CMC PROVIDES FOR CORRECTED, CALCULATION OF 37.9MG/ML CORRECTED STATEMENTS OF QUANTITATIVE COMPOSITION, A CORRECTED REPRESENTATIVE LABEL FOR CLINICAL SUPPLIES AND THE RATIONAL FOR LACK OF IMPACT ON THE DEVELOPMENT OF WIN 59010-2 INJECTION.
22-JUN-94	TEL		V-43	DR. BLAY WAS CONTACTED TO OBTAIN REVIEWING, PHARMACOLOGIST'S RATIONALE FOR RECOMMENDING A REEVALUATION OF 59010 TERATOGENIC POTENTIAL IN THE RABBIT.
22-JUN-94	TEL		V-43	AFTER DISCUSSING WITH DR. SEE HIS REASON, FOR RECOMMENDING A REEVALUATION FOR TERATOGENIC POTENTIAL OF 59010 IN THE RABBIT, HE STATED HE WILL RECOMMEND THAT THE NDA FOR WIN 59010-2 'NOT' BE APPROVED IF THERE IS NOT A VALID SECOND PIVOTAL TERATOLOGY STUDY.
23-JUN-94	TEL		V-43	FDA CALLED WITH MEDICAL REVIEWER'S COMMENT, FOR SERIAL NO. 054 WHICH WAS THE PROPOSAL FOR THE SERUM IRON STUDY. FDA INDICATED THAT A SALINE PLACEBO IS NEEDED FOR THIS STUDY.
24-JUN-94	SUB	064	V 43	NP/NI: DR. ZINNY FOR PROTOCOL 59010-2-006, DRA SUBMITTED THE FOLLOWING NEW INVESTIGATOR INFORMATION: . DR. ANDERSON FOR PROTOCOL 59010-2-003 . DR. RUBIN FOR PROTOCOL 59010-2-004. . LISTED ARE NEW SUBINVESTIGATORS FOR PROTOCOLS 59010-2-002 AND 59010-2-003
29-JUN-94	SUB	065	V-43	ANNUAL REPORT PROVIDES INFORMATION OBTAINED, DURING THE TIME PERIOD OF 05-APR-93 TO 04-APR-94.
07-JUL-94	TEL		V-43	FDA CALLED AND COMMENTED THAT SINCE, ADVERSE DRUG REACTIONS ARE BEING MONITORED, PROTOCOL 59010-2-006 SHOULD BE BLINDED. PAGE 13 OF THE PROTOCOL

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07-JUL-94	TEL		V-43	PROVIDES A THIRD PARTY BLIND. DR. BLAY WILL BRING THIS TO THE ATTENTION OF THE MEDICAL REVIEWER TO DETERMINE IF THAT SATISFIES THE FDA'S REQUEST.
15-JUL-94	SUB	066	V-43	GC: DRA PROVIDED MINUTES OF 02-JUN-94, TELEPHONE CONFERENCE, WHICH WAS HELD TO CLARIFY COMMENTS RECEIVED BY STERLING IN FDA'S 03-MAY-94 LETTER REGARDING SERIAL NO. 053.
21-JUL-94	SUB	067	V-44	NEW INVESTIGATORS AND INFO.AMEND: CLINICAL, DRS. BROWN, PATT, AND SELTZER FOR PROTOCOL 59010-2-003. DRS. SEMELKA AND SMALL FOR PROTOCOL 59010-2-004. DRA SUBMITTED A REVISED CLINICAL INVESTIGATOR BROCHURE DATED 15-JUN-94 TO REPLACE THE 27-APR-93 VERSION.
26-JUL-94	SUB	068	V-45	INFO.AMEND: PHARM/TOX PROVIDES FOR THREE, FINAL STUDY REPORTS.
29-JUL-94	FAC		V-45	FDA FAXED THE FOLLOWING CLINICAL COMMENTS, AND REQUEST: . ON SITE READINGS AND READER ASSESSMENT OF AGREEMENT OF FINAL INTERPRETATIONS ARE NOT ACCEPTABLE SINCE BLINDING IS NOT ADEQUATE . THE FDA MAY WISH TO PERFORM ITS OWN READINGS IN A SELECTED PATIENT POPULATION . SINCE THESE SCANS ARE TO IDENTIFY TISSUE TYPE, PLEASE ENSURE THAT THE PROTOCOLS PROVIDE FOR TISSUE CONFIRMATION
08-AUG-94	SUB	069	V-45	PC/NSI: PROTOCOLS 59010-2-003,A-03 AND, 59010-2-004,A-03 PROVIDE SPECIFIC ASSESSMENTS OF SAFETY PARAMETERS BY DEFINING CLINICALLY RELEVANT CHANGES FOR VITAL SIGNS. ADD GGT, A BILIARY EXCRETORY ENZYME SPECIFIC FOR HEPATIC DISEASE, TO THE CHEMISTRY PROFILE. CHANGE THE TIME BETWEEN CECT WITH AN IODINATED CONTRAST AGENT AND THE INJECTION OF WIN 59010-2 TO PERMIT MORE PRECISE DETERMINATIONS OF ATTRIBUTION OF AN ADVERSE EVENT TO A SPECIFIC AGENT.

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08-AUG-94	SUB	069	V-45	DRA PROVIDED CHANGES TO THE SUBINVESTIGATORS CONDUCTING PROTOCOLS 59010-2-003 AND 59010-2-006.
09-AUG-94	SUB	070	V-45	RESPONSE TO FDA REQUEST FOR INFORMATION, DATED 03-MAY-94. DRA HAS RESTATED FDA'S COMMENTS IN BOLD FOLLOWED BY STERLINGS RESPONSES.
10-AUG-94	SUB	071	V-45	RESPONSE TO FDA REQUEST FOR INFORMATION, DATED 29-JUL-94. DRA PROVIDED RESPONSES TO THE FOLLOWING: . ON-SITE READINGS AND READER ASSESSMENT OF AGREEMENT OF FINAL INTERPRETATIONS ARE NOT ACCEPTABLE SINCE BLINDING IS NOT ADEQUATE . THE FDA MAY WISH TO PERFORM ITS OWN READINGS IN A SELECTED PATIENT POPULATION . SINCE THESE SCANS ARE TO IDENTIFY TISSUE TYPE, PLEASE ENSURE THAT THE PROTOCOL PROVIDE FOR TISSUE CONFIRMATION
17-AUG-94	TEL		V-45	DR. JONES CALLED IN REFERENCE TO SERIAL NO., 069, DATED 08-AUG-94. HE WAS LOOKING FOR THE AMENDMENT THAT WAS REFERRED TO IN THE COVER LETTER. DRA DIRECTED HIM TO THE FOUR PAGES FOLLOWING THE FORM FDA 1571. DRA INQUIRED IF THEY WERE MISSING FROM HIS COPY. HE INDICATED THEY WERE NOT MISSING AND EVERYTHING WAS IN ORDER.
09-SEP-94	TEL		V-45	MR. ROSOFF WAS CONTACTED FOR CLARIFICATION, REGARDING EXPORTING MATERIALS FROM FOREIGN TRADE ZONE. HE INFORMED DRA THAT REGULATED PRODUCTS IN FOREIGN TRADE ZONES MUST COMPLY WITH THOSE LAWS THAT COME WITHIN THE PURVIEW OF FDA.
15-SEP-94	TEL		V-45	FDA EXPRESSED INTERESTRED IN A DEMONSTRATION, OF BLINDED READ PROCEDURE. DATES AND DETAILS WILL FOLLOW. DRA BROUGHT FDA UP TO DATE ON THE STATUS OF THE PRE-NDA MEETING PACKAGE.
23-SEP-94	TEL		V-45	FDA WOULD PREFER A LETTER FOR DR. JONES, TO OUTLINE WHAT THE NATURE OF THE DEMONSTRATION BY BIO-IMAGING WOULD BE, PREFERABLE SPEICIFIC TO THE

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23-SEP-94	TEL		V-45	MANGAFODIPIR TRISODIUM PROJECT. FDA INFORMED DRA THAT COMMENTS TO IND AMENDMENTS, SERIAL NUMBERS 070, AND 071 (INCLUDING FDA'S WISH TO CONDUCT THEIR OWN READINGS) ARE WITH DR. LOVE.
30-SEP-94	SUB	072	V-45	GC: DRA INFORMED FDA THAT AS OF 01-OCT-94, OWERSHIP OF THE PHARMACEUTICAL ASSETS OF STERLING WINTHROP INC. IS TRANSFERRED TO NYCOMED IMAGING AS.
01-OCT-94	SUB	073	V-45	GC: DRA INFORMED FDA THAT AS OF 01-OCT-94, NYCOMED INC. ACCEPTS THE TRANSFER OF THE SPONSORSHIP OF IND 33,031 FROM STERLING WINTHROP INC.
12-OCT-94	SUB	074	V-46	DRA SUBMITTED PRE-NDA PACKAGE AND REQUESTED, A MEETING TO DISCUSS THE FORMAT OF THE NDA TO BE SUBMITTED IN THE FIRST HALF OF 1995.
13-OCT-94	LFF		V-47	FDA HAS COMPLETED REVIEW OF SUBMISSIONS, SERIAL NOS. 070 AND 071 RESPECTIVELY DATED AUGUST 9 AND 10, 1994. SERIAL NO. 070 PROVIDED DRA'S COMMENTS TO FDA LETTER DATED 03-MAY-94 AND SERIAL NO. 071 PROVIDED DRA'S COMMENTS TO FDA'S FAX DATED JULY 29, 1994. FDA LISTED COMMENTS AND REQUEST FOR ADDITIONAL INFORMATION (SEE LETTER).
13-OCT-94	TEL		V-47	FDA ACKNOWLEDGED RECEIPT OF DRA'S PRE-NDA, MEETING REQUEST AND INFORMATION PACKAGE. FDA ASKED DRA TO CALL WEDNESDAY, 19-OCT-94 TO OBTAIN THE MEETING DATE. FDA STATED THE PACKAGE APPEARS WELL ORGANIZED.
19-OCT-94	TEL		V-47	FDA INFORMED DRA THAT THE MEETING DATE FOR, THE PRE-NDA MEETING WILL BE TUESDAY, 29-NOV-94.
26-OCT-94	TEL		V-47	FDA INFORMED DRA THAT THE TIME FOR THE, PRE-NDA MEETING HAS BEEN TENTATIVELY SCHEDULED FOR 11:00 AM - 12:00 PM ON 29-NOV-94. DRA IS TO CONFIRM THIS TIME WITH DR. BLAY THE WEEK OF 31-OCT-94.

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01-NOV-94	TEL		V-47	FDA CALLED DRA TO CONFIRM PRE-NDA MEETING, WHICH WILL BE HELD ON TUESDAY, 29-NOV-94 AT 11:00 AM IN CONFERENCE ROOM G. ATTENDING FROM FDA WILL BE: DRS. LOVE, BOTSTEIN, JONES, SCHEINIEN, SEE, COONEY, SMITH, HUNT, AND VINCENT. ONE REVIEWING MEDICAL OFFICER AND ONE REVIEWING CHEMIST.
18-NOV-94	LFF		V-47	FDA ACKNOWLEDGE NOTIFICATION OF THE, TRANSFER OF SPONSORSHIP AND HAVE REQUESTED THE FOLLOWING IN ORDER TO COMPLETE THE CHANGE IN OWNERSHIP: . A SUMMARY OF THE TRAINING AND EXPERIENCE OF THE NEW MONITOR OF THE IND . A COMMITMENT TO AMEND THE IND WITHIN 60 DAYS TO COVER ALL CHANGES IN THE IND RESULTING FROM NEW OWNERSHIP AND TO PROVIDE FOR SUBSEQUENT CHANGES BY AMENDMENTS IN ACCORDANCE WITH THE IND REGULATIONS . A COMMITMENT TO INFORM ALL ACTIVE INVESTIGATORS OF THE CHANGE, AND TO OBTAIN AN UPDATED FORM FDA 1572 AND COMMITMENTS TO YOURSELF AS THE NEW SPONSOR . A LIST OF ALL ACTIVE INVESTIGATORS OR A STATEMENT THAT THEY ARE THE SAME AS CURRENTLY LISTED IN THE IND, IF THAT BE THE CASE . ANY CHANGES IN STUDY PROTOCOLS OR OTHER STUDY PARAMETERS
22-NOV-94	TEL		V-47	THE LOGISTICS OF THE PRE-NDA MEETING WERE, DISCUSSED.
29-NOV-94	FAC		V-52	FDA FAXED PRE-NDA MEETING MINUTES TO, NYCOMED.PRE-NDA MEETING DATE 29-NOV-95.
30-NOV-94	SUB	075	V-47	RESPONSE TO FDA REQUEST FOR INFORMATION, DATED 13-OCT-94. DRA PROVIDED RESPONSES TO FDA COMMENTS REGARDING SERIAL NOS. 070 AND 071.
15-DEC-94	SUB	076	V-47	DRA PROVIDED MINUTES OF PRE-NDA MEETING, AND COPIES OF THE OVERHEADS PRESENTED DURING THE MEETING. DRA REQUESTED A COPY OF ANY MINUTES THAT THE AGENCY MAY GENERATE FROM THE MEETING.

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19-DEC-94	TEL		V-47	DRA CALLED FDA TO SEEK CLARIFICATION ON THE, NEED FOR UPDATED FORM FDA 1572'S AS OUTLINED IN POINT #3 OF THE 18-NOV-94 LETTER FROM FDA. FDA STATED THAT THERE IS NO NEED TO UPDATE THE FORM FDA 1572 SINCE THERE IS NOT CHANGE IN THE STUDY PROTOCOLS OR OTHER STUDY PARAMETERS.
21-DEC-94	TEL		V-47	FDA ASKED DRA TO SEND A LETTER TO FDA, SUMMARIZING OUR EXPECTATIONS IN ADVANCE OF A CANDA MEETING WITH THE MEDICAL REVIEWING OFFICERS. DR. BLAY ACKNOWLEDGED RECEIPT OF OUR MINUTES OF THE PRE-NDA MEETING AND WILL DISTRIBUTE TO ALL THE ATTENDEES. IF FDA HAS ANY CONCERNS REGARDING THE MINUTES, WE WILL BE CONTACTED.
29-DEC-94	SUB	077	V-47	GC: IN REFERENCE TO THE CHANGE IN SPONSOR, AND TO FDA LETTER OF 18-NOV-94. DRA PROVIDED THE FOLLOWING: CHANGE IN MEDICAL MONITOR: . DR. JASON ZIELONKA WILL SERVE AS THE PERSON RESPONSIBLE FOR REVIEWING AND EVALUATING THE SAFETY IN INVESTIGATION CONDUCTED UNDER THIS IND . DR. RONALD ROBISON WILL SERVE AS THE PERSON RESPONSIBLE FOR MONITORING THE CONDUCT AND PROGRESS OF THE CLINICAL INVESTIGATIONS UNDER THIS IND IND COMMITMENTS: . ANY CHANGES IN THE IND RESULTING FROM NEW OWNERSHIP WILL BE MADE WITHIN 60 DAYS INVESTIGATOR NOTIFICATION: . ALL INVESTIGATORS HAVE BEEN NOTIFIED OF CHANGE IN OWNERSHIP LIST OF INVESTIGATORS: . THE LIST OF ACTIVE INVESTIGATORS IS THE SAME AS THOSE CURRENTLY LISTED IN THE IND PROTOCOL CHANGES: . THERE ARE NO CHANGES IN STUDY PROTOCOLS OR STUDY PARAMETERS
19-JAN-95	TEL		V-47	DRA AND FDA DISCUSSED SERIAL NO. 075, SUBMITTED 30-NOV-94, WHICH CONTAINED RESPONSES TO FDA COMMENTS ON PROTOCOLS 003 AND 004, SPECIFICALLY ON OUR

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19-JAN-95	TEL		V-47	RESPONSE TO THE AGENCY'S REQUEST TO DISTINGUISH BETWEEN CONVENTIONAL AND SPIRAL CECT. WE WERE WARNED TO DOWNPLAY THE DEMONSTRATION OF EQUIVALENCY OF HELICAL AND SPIRAL CT SCANNERS.
20-JAN-95	SUB	078	V-47	DRA REQUESTED A CONFERENCE TO PROVIDE THE, AGENCY WITH A CANDA DEMONSTRATION. DRA PROVIDED FDA WITH A TENTATIVE AGENDA AND AVAILABLE DATES FOR SUCH A MEETING. DRA WILL CONTACT FDA WITHIN TWO DAYS OF RECEIPT OF THIS LETTER TO CONFIRM A MEETING DATE.
25-JAN-95	TEL		V-47	FDA RETURNED DRA'S CALL TO DISCUSS TWO ITEMS, . NO NEWS ON "OFFICAL" MINUTES OF THE PRE-NDA MEETING . CANDA DEMONSTRATION ARRANGEMENTS ONGOING, MAY NOT BE THE WEEK OF FEBRUARY 6
27-JAN-95	TEL		V-47	DR. BLAY CALLED TO DISCUSS IF ANY PROGRESS, HAD BEEN MADE REGARDING THE CANDA DEMONSTRATION, TIME, ATTENDEES, ETC.
31-JAN-95	TEL		V-47	FOLLOW-UP CALL TO DETERMINE IF ANY PROGRESS, WAS MADE ON SCHEDULING THE CANDA DEMONSTRATION. THE MEETING IS TENTATIVELY SCHEDULED FOR MONDAY, 27-FEB-95, FROM 1 - 4 PM.
08-FEB-95	TEL		V-47	CANDA DEMONSTRATION MEETING WITH FDA IS, CONFIRMED FOR MONDAY FEBRUARY 27, 1995 FROM 1:00 PM - 3:00 PM IN THE PARKLAWN BUILDING, CONFERENCE ROOM 18B24
09-FEB-95	SUB	079	V-47	GC: DR. SCHEININ EXPRESSED INTEREST IN, RECEIVING, IN ADVANCE OF THE NDA, CERTAIN INFORMATION PERTAINING TO THE CMC SECTION. AT THIS TIME DRA PROVIDED THIS INFORMATION TO FDA.
16-FEB-95	FAC		V-47	FDA FAXED DRAFT CLINICAL COMMENTS LISTED, . POST-DOSING ECGS SHOULD BE PERFORMED AS PREVIOUSLY SUGGESTED . AFTER APPROVAL OF THIS AGENT, A WIDE VARIETY OF IMAGING

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16-FEB-95	FAC		V-47	EQUIPMENT; I.E., FIELD STRENGTHS WILL BE UTILIZED. THE SPONSOR SHOULD DETERMINE IF THE DEGREEE OF ENCHANCEMENT IS DEPENDENT ON MAGNETIC FIELD STRENGTH AND IF DIFFERENT FIELD STRENGTHS REQUIRE DIFFERENT DOSING REGIMENTS . DEMONSTRATE THAT CT IS EQUIVALENT TO SPIRAL CT . DEMONSTRATE THAT CECT IS EQUIVALENT TO SPIRAL CECT
22-FEB-95	TEL		V-47	FDA CALLED TO CONFIRM THE CANDA MEETING, FOR 1:00 PM ON MONDAY, 27-FEB-95. FDA EXPRESSED CONCERN THAT THE MEETING WOULD BE TOO LONG, HOWEVER, DRA STATED THAT MOST OF THE TIME WOULD BE A QUESTION AND ANSWER PERIOD REGARDING THE CANDA.
28-FEB-95	FAC		V-47	FDA FAXED DRAFT SUMMARY OF THE CONVERSATION, BETWEEN DRA AND DR. JONES, FOLLOWING THE CANDA MEETING, CONCERING THE USE OF SPIRAL/HELICAL CT IN CONJUCTION WITH UNIPHASIC/BIPHASIC INJECTIONS.
02-MAR-95	SUB	080	V-48	INFO. AMEND: PHAR/TOX PROVIDES FOR NINE, STUDY REPORTS.
06-MAR-95	TEL		V-49	DRA ASKED FOR THE TITLES OF NYCOMED, ATTENDEES AT LAST WEEK'S CANDA MEETING, ATTACHED TO THIS CONTACT IS THE LIST THAT WAS FAXED TO HIM ON 07-MAR-95
07-MAR-95	TEL		V-49	DRA ALERTED DR. BLAY TO THE FACSIMILE, BEING SENT REGARDING THE TITLES OF THE NYCOMED ATTENDEES AT THE CANDA MEETING,PER HIS REQUEST. DRA INQUIRED WHETHER DR. SHEININ HAD ANY COMMENTS TO SERIAL NO. 079, DATED 09-FEB-95. DRA INQUIRED WHETHER NYCOMED MAY HAVE A CONFERENCE CALL WITH DRS. JONES AND JU REGARDING THE AGENCY'S CONTINUING CONCERN WITH THE BLINDED READ PROCEDURE.
13-MAR-95	SUB	081	V-49	DRA PROVIDED HIGHLIGHTS WHICH SUMMARIZE, NYCOMED'S UNDERSTANDING OF THE DISCUSSIONS HELD DURING THE MEETING HELD ON MONDAY, 27-FEB-95 BETWEEN THE AGENCY AND NYCOMED INC. AT WHICH THE PROPOSED CANDA FOR THE UPCOMING NDA WAS DEMONSTRATED.

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13-MAR-95	TEL		V-49	DR. BLAY CALL REGARDING:, . DID DR. SCHEININ HAVE ANY QUESTIONS/COMMENTS TO NYCOMED'S SERIAL NO. 079 CONTAINING CMC INFORMATION IN ADVANCE OF THE NDA . DRS. JU AND JONES HAVE NO COMMENTS AT THIS TIME REGARDING OUR BLINDED READ PROCEDURES, SO ARE NOT WILLING TO PARTICIPATE IN A PHONE CONFERENCE . DR. NORMAN SEE WOULD LIKE TO SEE THE PRELIMINARY RESULTS OF THE REPEAT RABBIT TERATOLOGY STUDY IN WRITING BEFORE HE WILL DISCUSS THE ISSUE WITH US OVER THE PHONE.
16-MAR-95	LTF		V-49	DRA REQUESTS AOTHORIZATION FROM THE FDA, TO EXPORT 10MM MANAGAFODIPIR TRISODIUM INJECTION TO: HEGE S. LINDE, NYCOMED IMAGING AS, NYCOVEIEN 1-2, N-0485 OSLO, NORWAY.
27-MAR-95	SUB	082	V-49	GC: DRA PROVIDED PRELIMINARY, UNAUDITED, RESULTS OF THE TERATOGENICITY STUDY IN NEW ZEALAND WHITE RABBITS.
05-APR-95	TEL		V-49	DRA CONTACTED DR. BLAY REQUESTING A, PHONE CONFERENCE WITH DR. NORMAN SEE, REVIEWING PHARMACOLOGIST, REGARDING THE RABBIT TERATOLOGY STUDY WHICH WAS SUBMITTED IN SERIAL NO 082. DRA WILL INITIATE THE PHONE CONFERENCE EITHER APRIL 13, OR 14.
07-APR-95	LFF		V-49	LETTER OF AUTHORIZATION TO SHIP A TOTAL, OF 10,000 VIALS OF 10MM MANGAFODIPIR TRISODIUM INJECTION IN DIVIDED SHIPMENTS TO HEGE S. LUNDE IN NORWAY AND THE DEPARTMENT OF RADIOLOGY IN BELGIUM FOR THE PROPOSED CLINICAL TRIALS.
10-APR-95	TEL		V-49	DRA CALLED FDA AS A FOLLOW-UP TO SERIAL, NO. 082 WHICH CONTAINED THE PRELIMINARY RESULTS OF THE SECOND RABBIT TERATOLOGY STUDY. DR. SEE INDICATED THAT THE SECOND RABBIT TERATOLOGY STUDY WILL MEET THE TERATOLOGY REQUIREMENTS FOR THE NDA.

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24-APR-95	TEL		V-49	DR. SALAZAR, CHEMISTRY REVIEWER, CALLED DRA, AND DISCUSSED THE FOLLOWING: . STABILITY MATRIX SUBMITTED 2/9/95 IS NOT ACCEPTABLE; THEY THOUGHT 6 BATCHES OF DRUG PRODUCT WOULD BE SUBMITTED, NOT 3 . IN THE TEMPLATE FOR REPORTING STABILITY DATA, DESCRIBE THE STORAGE POSITIONS OF THE VIALS; INCLUSION OF SOME IN AN INVERTED POSITION IS REQUIRED FOR ALL PARENTERAL DRUGS . REMIDER TO INCLUDE EXTRACTABLE DATA ON BOTH STOPPERS; IT WAS NOT APPARENT IN THE PRE-NDA DOCUMENTS WHERE IT WOULD BE LOCATED. . FOLLOW-UP TELEPHONE CALL WILL BE PLACED WITHIN ONE WEEK RESOLVE THE MATRIX ISSUE.
03-MAY-95	SUB	083	V-50	INFO.AMEND: PHARM/TOX PROVIDES FOR SEVEN (7), STUDY REPORTS.
05-MAY-95	SUB	084	V-51	DRA REQUESTED AN EXTENSION TO THE, SUBMISSION OF THE ANNUAL REPORT DUE TO THE FACT THAT RESOURCES WHICH WOULD NORMALLY SUPPORT THE PREPARATION OF THE IND ANNUAL REPORT ARE CURRENTLY ENGAGED IN THE PREPARATION OF AN NDA FOR MANGAFODIPIR
19-MAY-95	SUB	085	V-51	GC: DRA NOTIFIED FDA THAT EFFECTIVE, IMMEDIATELY, NYCOMED INC. HAS MOVED TO A NEW LOCATION IN WAYNE, PA.
14-JUN-95	SUB	086	V-51	NP/NI: DR. COURT FOR PROTOCOL 59010-02-008, DRA PROVIDED CASE REPORT FORMS FOR PROTOCOL 59010-2-008, DATED 04-MAY-95
14-JUN-95	TEL		V-51	DRA CALLED TO CONFIRM THE VERSION OF, WORDPERFECT FDA EXPECTS FOR THE NDA. DR. BLAY STATED THAT NYCOMED SHOULD SUBMIT THE WORDPERFECT 6.0 DISKS FOR THIS NDA. DRA AND FDA DISCUSSED THE CHEMISTRY REVIEWERS' (DR. SALAZAR) COMMENTS PHONED IN APRIL. DRA ALERTED FDA TO SOME OF THE CMC CHANGES NYCOMED IS MAKING SINCE THE PACKAGE WAS SUBMITTED TO DR. SALAZAR (SERIAL NO. 079, 09-FEB-95).

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14-JUN-95	TEL		V-51	DR. BLAY SUGGESTED TO CONTACT DR. SALAZAR DIRECTLY.
19-JUN-95	TEL		V-51	DR. PIERRO REQUESTED A WP 6.0 DISK, CONTAINING THE PHARMACOKINETICS STUDY PROTOCOL WHICH WAS SUBMITTED RECENTLY
20-JUN-95	TEL		V-51	DRA CALLED DR. PIERRO TO ALERT HIM THAT, NYCOMED WOULD BE SENDING HIM PROTOCOL 59010-2-008 ON A WORD PERFECT VERSION 5.2 DISKETTE RATHER THAN VERSION 6.0 AS HE REQUESTED
21-JUN-95	SUB	087	V-51	RESPONSE TO FDA REQUEST DATED 19-JUN-95, DRA PROVIDED DR. PIERRO A WORDPERFECT 5.2 DISKETTE CONTAINING A COPY OF PROTOCOL 59010-2-008.
22-JUN-95	SUB	088	V-51	GC: CHANGE IN SAFETY MONITOR, DRA INFORMED, FDA THAT RONALD ROBISON M.D. WILL NOW SERVE AS THE PERSON RESPONSIBLE FOR REVIEWING AND EVALUATING THE SAFETY IN INVESTIGATIONS CONDUCTED UNDER THIS IND.
22-JUN-95	TEL		V-51	DRA INFORMED FDA OF A THREE(3) DAY, REPORTABLE SERIOUS ADVERSE EVENT WHICH OCCURED IN PATIENT #0036.
06-JUL-95	SUB	089	V-51	SAFETY REPORT FOR PATIENT #036 WHO WAS, ENROLLED INTO NYCOMED STUDY MNV005 IN BELGIUM. PATIENT DIED.
11-JUL-95	SUB	090	V-51	PC/NI: PROTOCOL 59010-2-008, A-01, PROVIDES FOR: 1. THE DESIGNATED MEDICAL MONITOR HAS BEEN RESIGNED 2. ADDITIONAL FECAL DYE MARKER IS BEING ADDED TO THE TWO PREVIOUSLY SCHEDULED MARKERS. THIS MARKER WILL BE INGESTED ON THE MORNING OF STUDY DAY 9 PRIOR TO BREAKFAST IN ORDER TO MONITOR FECAL TRANSPORT 3. EACH SUBJECT'S BODY WEIGHT WILL BE MONITORED TO ASSESS POSSIBLE CHANGE IN BODY WEIGHT DUE TO THE STRICT DIET AND LIMITATIONS TO THE SUBJECT'S NORMAL PHYSCIAL ACTIVITY DURING CONFINEMENT IN THE STUDY SITE. TRENDS IN BODY

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11-JUL-95	SUB	090	V-51	WEIGHT CHANGES WOULD DICTATE THE SUBJECT'S ACCESS TO CALORIC FOODS 4. PLATELETS WERE INADVERTENTLY OMITTED FROM THE LIST OF HEMATOLOGY PARAMETERS BEING MEASURED IN THIS STUDY NEW INVESTIGATOR: DR. MORGNAROTH FOR PROTOCOL 59010-2-008
13-JUL-95	FAC		V-51	DRA FAX A SUMMARY TO CONFIRM THE, TELEPHONE CONFERENCE HELD IN THE MORNING TO DISCUSS THE CANDA AND THE HARDWARE.
13-JUL-95	TEL		V-51	FDA INFORMATION SYSTEMS WAS CONTACTED, TO DISCUSS CANDA HARDWARE.
14-JUL-95	FAC		V-51	FDA SENT FAX REGARDING PHASE I STUDY, OF MANGAFODIPIR'S PHARMACOKINETICS AND SAFETY. (SEE CONTACT REPORT)
14-JUL-95	FAC		V-51	DRA FAXED QUESTIONS AND COMMENTS REGARDING, THE DATA FROM THE FRIST PK STUDY.
21-JUL-95	TEL		V-51	FDA INFORMED DRA THAT NYCOMED'S CANDA, SUBMISSION PROPOSAL FOR HARDWARE DELIVERY IS ACCEPTABLE TO FDA.
24-JUL-95	FAC		V-51	FDA FAXED DRAFT CLINICAL COMMENTS, REGARDING PROTOCOL 59010-2-008, SERIAL NO. 086.
28-JUL-95	TEL		V-51	MULTIPLE CONTACTS: . 28-JUL-95: DR. CHOW CALLED TO CONFIRM IF DRA HAS RECEIVED HIS FAX WHICH INCLUDED COMMENTS ABOUT THE PHARACOKINETICS PROTOCOL. HE ASKED WHEN RESPONSES TO THESE COMMENTS WOULD BE AVAILABLE. DRA INFORMED HIM THAT CLINICAL WAS IN THE PROCESS OF DRAFTING RESPONSES AND THAT WE WOULD RESPOND SOMETIME IN EARLY AUG. DR. CHOW STATED THAT THESE ARE STRICLY UNOFFICAL COMMENTS AND THAT RESPONSES SHOULD BE FORWARDED DIRECTLY TO HIM, AND NOT TO THE AGENCY, . 31-JUL-95: DR. CHOW CALLED WITH THREE COMMENTS ON OUR RECENT SUBMISSION (SERIAL NUMBER 090), REGARDING CHANGE

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28-JUL-95	TEL		V-51	IN PROTOCOL 59010-2-008.
31-JUL-95	TEL		V-51	DR. CHOW ASKED DRA TO IGNORE HIS FAX, OF 14-JUL-95.
18-AUG-95	TEL		V-51	THE TESLASCAN (MANGAFODIPIR TRISODIUM), INJECTION NDA WAS ASSIGNED # 20-652.
11-SEP-95	SUB	091	V-51	PA: DR. MORGANROTH SUMBITTED A REVISED, UPDATED FORM FDA 1572 WHICH REMOVES DRS. BLACK AND BELLARY AS SUBINVESTIGATORS.
13-SEP-95	SUB	092	V-51	RESPONSE TO REQUEST FOR INFORMATION DATED, 24-JUL-95. DRA PROVIDED RESPONSES TO THE FOLLOWING CLINICAL COMMNETS: . THE TRIAL SHOULD EMPLOY A PLACEBO . THE ADVERSE EVENTS SECTION IS INADEQUEATE. BECAUSE THERE IS NO PLACEBO OR COMPARATOR EMPLOYED IN THE TRIAL, ALL EVENTS WILL BE CONSIDERED BY FDA REVIEWERS AS BEING ATTRIBUTABLE TO MANGAFODIPIR, PARTICULARLY THOSE EVENTS LISTED UNDER THE "UNLIKELY" AND "UNKNOWN CATEGORIES" . IN SECTION 5.6 (PHARMACOKINETIC SERUM/PLASMA PROFILE), THE SAMPLING TIMES DO NOT MATCH CASE REPORT FORM PAGE 23; THE LATTER HAS A 24 HOUR PRIOR TIMEPOINT BUT IS MISSING THE 48 AND 72 HOUR POST-DOSING TIMEPOINTS . PLEASE PROVIDE ADDITIONAL INFORMATION ON THE ALLOWED DIET AND ANYTIME-RELATED EFFECTS OF INTAKE AND FECAL EXCRETION . PLEASE INDICATE IF THE DIET FOR LIVER IMPAIRED PATIENTS IS THE SAME AS THAT FOR NORMALS . DURTHER ASSESSMENT OF THE SUBGROUP SAMPLE SIZE IS NEEDED THE GROUPS ARE UNBALANCED IN TERMS OF NUMBERS, AND THUS, WILL PROBABLY ONLY PROVIDE INFORMATION ON TRENDS
27-SEP-95	SUB	093	V-52	ANNUAL REPORT PROVIDES INFORMATION OBTAINED, DURING THE TIME PERIOD 05-APR-94 TO 04-APR-95. ALSO INCLUDED IS THE CLINICAL INVESTIGATOR BROCHURE WHICH WAS REVISED 19-AUG-94

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Date	Comm.Type	Serial No.	Location	Abstract
15-NOV-95	FAC		V-52	FDA FAXED PRE-NDA MEETING MINUTES FOR, IND 33,031. PRE-NDA MEETING SCHEDULED FOR 29-NOV-95.
30-NOV-95	SUB	094	V-52	INFO AMEND: PHARM/TOX, FOURTEEN STUDY REPORTS WERE PREIVIOULY SUBMITTED TO THE FDA AS PART OF THE TESLASCAN NDA ON 08-SEP-95. DRA PROVIDED A TABLE WHICH LISTS THE DISCIPLINE, TITLE, AND LOCATION FOR EACH OF THE PRECLINICAL STUDY REPORTS WITHIN THE NDA.
05-JAN-96	TEL		V-52	FDA CALLED REGARDING SERIAL NO. 090, CLINICAL PROTOCOL 59010-2-008/AMENDMENT. FDA INQUIRED ABOUT THE STATUS OF THE STUDY. DRA INDICATED THE PATIENT ENROLLMENT WAS COMPLETE, CLINICAL LAB SPECIMEN ANALYSIS WAS CONCLUDING AND THE TARGET DATE FOR SUBMISSION OF THE FINAL CLINICAL REPORT WAS MID-END OF MARCH 1996.
04-APR-96	TEL		V-52	DR. PIERRO REQUESTED AND ELECTRONIC VERSION, OF THE 1994 MANGAFODIPIR IND ANNUAL REPORT.
10-APR-96	SUB	095	V-52	RESPONSE TO FDA REQUEST FOR INFORMATION, DATED 04-APR-96. DRA PROVIDED DR. PIERRO WITH A DISKETT CONTAINING THE ANNUAL REPORT FOR TESLASCAN.
15-APR-96	TEL		V-52	DRA CONTACTED DR. PIERRO TO DETERMINE, IF HE AD RECEIVED THE TESLASCAN ANNUAL REPORT DISKEET WHICH WAS SUBMITTED ON 10-APR-96. DR. PIERRO INDICATED THAT IT WAS NOT INCLUDED WITH THE INFORMATION HE RECEIVED. DRA EXPLAINED THAT THE DISKETTE FOR THE ANNUAL REPORT WAS SUBMITTED TO THE IND AND WAS NOT PART OF THE NDA INFORMATION. DR. PIERRO ASK IF DRA COULD SEND HIM ANOTHER DISKETTE. DRA AGREED.
16-APR-96	SUB	096	V-52	RESPONSE TO FDA REQUEST FOR INFORMATION, DATED 15-APR-96. DRA SENT DR. PIERRO A DISKETTE CONTAINING THE ANNUAL REPORT FOR IND 33031.
17-JUN-96	TEL		V-52	FDA CALLED TO ASK IF ANY NEW CLINICAL, INFORMATIN WAS GOING TO BE INCLUDED IN THE UP-COMING ANNUAL REPORT. DRA STATED THAT THE ONLY CLINICAL

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17-JUN-96	TEL		V-52	INFORMATION COVERED IN THE ANNUAL REPORT RELATED TO THE 59010-2-008 PK STUDY. IN LIGHT OF THIS, THE MEDICAL REVIEWER WOULD SIGN-OFF ON HIS MEDICAL REVIEW OF NDA 20-652 AND SEND IT TO MANAGEMENT. FDA INDICATED THERE WERE A FEW QUESTIONS FROM OTHER REVIEWERS.
16-JUL-96	SUB	097	V-52	DRA SUBMITTED TO FDA THE ANNUAL REPORT, PROVIDING INFORMATION OBTAINED DURING THE TIME PERIOD 05-APR-95 TO 04-APR-96.
27-AUG-96	SUB	098	V.53-56	INFO AMEND: PRE-CLINICAL PROVIDES FOR THE, FOLLOWING STUDY REPORTS: . FOURTEEN STUDY REPORTS WHICH WERE PREVIOUSLY SUBMITTED AS PART OF THE TESLASCAN NDA ON 08-SEP-95 . ELEVEN STUDY REPORTS WHICH WERE PREVIOUSLY SUBMITTED AS PART OF AMENDMENT 2.1 OF NDA 20-652 ON 29-MAR-96 . TEN NEW STUDY REPORTS
10-JUN-97	SUB	099	V-57	SUBMITTED THE ANNUAL REPORT FOR THE PERIOD OF 4/5/96 - 4/4/97. INCLUDED IN THIS SUBMISSION IS THE INFORMATION FROM NON-IND CLINICAL STUDIES CONDUCTED IN EUROPE BY NYCOMED A.S., OSLO, NORWAY. THE FORM FDA 1571 AND TABLE OF CONTENTS ARE ATTACHED.

EXHIBIT 5B

BRIEF DESCRIPTION OF SIGNIFICANT ACTIVITIES: NDA LOG

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		25-JAN-95	TEL	V-96	DR. PIERRO STATED THE DISKETTE DRA SENT ON, 22-JAN-96 WAS UNREADABLE IN THE FORMAT PROVIDED. ROCCO BALLERINI STATED HE WOULD REFORMAT THE DATA AND PROVIDE A NEW DISK.
		18-AUG-95	TEL	V-1	THE TESLASCAN (MANGAFODIPIR TRISODIUM), INJECTION NDA WAS ASSIGNED 20-652.
		08-SEP-95	SUB	V-2-88	SUBMITTED NEW DRUG APPLICATION FOR, TESLASCAN (MANGAFODIPIR TRISODIUM) INJECTION.
		13-SEP-95	TEL	V-89	THE CSO STATED THE NDA HAD BEEN RECEIVED, BY THE DIVISION AND IT WAS LIKELY THAT DR. SANFORD WILLIAMS WOULD PROBABLY BE THE MEDICAL REVIEWER. A NEW CSO WILL BE ASSIGNED SINCE DR. ROY BLAY WILL MOVE TO DENTAL DRUG PRODUCTS.
		15-SEP-95	TEL	V-89	SANFORD WILLIAMS CALLED TO INTRODUCE HIMSELF, AND CONFIRM RECEIPT OF NDA 20-652. ALSO, FDA HAS NOT YET RECEIVED CONFIRMATION OF USER FEE CHECK. INDICATION WAS MADE THAT USER FEE CHECK WAS SENT.
		18-SEP-95	TEL	V-89	DR. CHOW CALLED AND EXPRESSED THAT THIS, WAS AN UNOFFICIAL, PERSONAL CALL. HE EXPECTS TO RECEIVE THE NDA WITHIN THE NEXT FEW DAYS. HE EXPRESSED CONCERN THAT THE CANDA EQUIPEMENT HAD NOT YET BEEN DELIVERED TO FDA. DR. CHOW SEEMED VERY CONCERNED THAT THE FDA CLOCK HAS ALREADY STARTED TICKING AND HE REQUIRES CANDA TRAINING. DR. CHOW ALSO REQUESTED AND SBA ON DISKETTE BE SENT TO HIM, DRA WILL DISCUSS THIS MATTER.
		18-SEP-95	TEL	V-89	FDA RETURNED DRA'S CALL OF 15 SEP 95., DRA ASKED WHEN FDA WOULD LIKE THE CANDA TO BE DELIVERED BEFORE OR AFTER FILING OF THE NDA. FDA STATED DELIVERY DATE WOULD BE DISCUSSED AND CSO WOULD CONTACT DRA WITH FURTHER INFORMATION.
		19-SEP-95	TEL	V-89	DR. DAVID PLACE CALLED TO INTRODUCE HIMSELF, AS THE ASSIGNED REVIEWER FOR THE CHEMISTRY, MANUFACTURING

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		19-SEP-95	TEL	V-89	AND CONTROLS SECTION OF THE MANGAFODIPIR NDA. DR. PLACE REQUESTED THE CHEMISTRY, MANUFACTURING AND CONTROLS SECTION ON DISKETTE IN WORDPERFECT 5.2 FORMAT ALONG WITH A LIST OF THE DIFFERENT FILES AND THE ASSOCIATED NDA VOLUMES/PAGES. DR. PLACE CALLED AGAIN AND LEFT A MESSGAGE REGARDING THE READINESS OF THE MANUFACTURING SITES.
		21-SEP-95	TEL	V-89	FDA RETURNED DRA'S CALL OF 20-SEP-95, DRA RESPONDED TO 2 REQUEST SPECIFIED DURING TELEPHONE CONTACT ON 19 SEPT 95. FDA REQUESTED CMC PORTION OF NDA ON DISKETTE. DRA STATED DISKETTES WITH CMC INFORMATION WOULD BE HAND DELIVERED ON 22-SEP-95. FDA INQUIRED AS TO THE PREPAREDNESS OF MANUFACTURING SITES FOR PRE-APPROVAL INSPECTION. DRA STATED THAT THE 2 SITES ARE READY FOR PRE-APPROVAL INSPECTION. FDA REQUESTED THAT NYCOMED SUBMIT A BRIEF LETTER STATING THAT THE SITES ARE READY FOR PRE-APPROVAL INSPECTION. FDA SUGGESTED THAT THIS LETTER WAS IMPORTANT FOR THE FILABILITY OF THE NDA.
		22-SEP-95	TEL	V-89	FDA CALLED CALLED TO INFORM NYCOMED THAT, THE DIVISION IS EXPECTING A LETTER FROM NYCOMED STATING THE ADDRESS AND PHONE NUMBER OF ALL COMMERCIAL SITES MANUFACTURING DRUG SUBSTANCE AND DRUG PRODUCT. THE LETTER SHOULD ALSO INDICATE THAT THESE SITES ARE READY FOR PREAPPROVAL INSPECTION. DRA ASKED IF RECEIPT OF THIS LETTER BY THE DIVISION WOULD AFFECT FILING OF NDA 20-652. CSO DID NOT KNOW.
		22-SEP-95	TEL	V-89	DRA CONFIRMED WITH MR. WILLIAMS THAT HE, IS THE NEW CSO. DRA AND FDA DISCUSSED THE TELEPHONE CONTACT OF 21-SEP-95 IN WHERE DAVID PLACE REQUESTED A LETTER INDICATING THAT THE MANUFACTURING SITES ARE READY FOR PRE-APPROVAL INSPECTION. FDA WILL TRY TO CLARIFY THIS REQUEST. DRA STATED THAT NYCOMED WOULD LIKE TO DELIVER THE CANDA ON 05-OCT-95. MR. WILLIAMS REQUESTED THAT NYCOMED SUPPLY HIM WITH PREVIOUS CONTACT REPORTS AND DRAFT LETTER TO THE FDA REGARDING THE CANDA.

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		22-SEP-95	TEL	V-89	FDA CALLED WITH QUESTIONS REGARDING THE, COMPUTER EQUIPMENT NECESSARY FOR THE BIOIMAGING COMPONENT OF THE CANDA. DRA AND BIOSTATISTICS CALLED FDA LATER IN THE DAY TO DISCUSS ANY UNANSWERED QUESTIONS REGARDING THE COMPUTER EQUIPMENT.
		25-SEP-95	LTF	V-89	DRA DOCUMENTED INFORMATION SUPPLIED TO THE, CHEMISTRY REVIEWER, DAVID PLACE ON 22-SEP-95. THIS INFORMATION INCLUDED DISKETTES CONTAINING THE CMC SECTION OF NDA 20-652 AND A TABLE INDEXING THE ELECTRONIC FILES TO THE PAPER NDA.
		26-SEP-95	LFF	V-89	FDA ACKNOWLEDGE RECEIPT OF NDA 20-652, DATE OF APPLICATION 08-SEP-95, DATE OF RECEIPT 15-SEP-95. THERAPEUTIC CLASSIFICATION - S. FDA STATED TO CITE THE NDA NUMBER AT THE TOP OF THE FIRST PAGE OF ANY COMMUNICATION CONCERNING THIS APPLICATION.
		26-SEP-95	TEL	V-89	DR. PLACE CALLED WITH CONFIRMATION, THAT THE DISKETTES OF CHEMISTRY, MANUFACTING AND CONTROLS SECTION WERE RECEIVED. DR. PLACE SUGGESTED NYCOMED SUBMIT A LETTER BEFORE THE 45 DAY FILING DATE THAT THE MANUFACTURING SITES ARE READY FOR PRE-APPROVAL INSPECTION. DRA STATED NYCOMED WOULD PREFER THAT ALL CONTACTS WITH THE FDA BE MADE DIRECTLY THROUGH CSO, MR. WILLIAMS, WHO HAS BEEN MADE AWARE OF THE REQUEST FOR THE PREAPPROVAL INSPECTION LETTER. DR. PLACE STATED THAT SINCE MANGAFODIPIR IS A "FAST-TRACK" DRUG THAT WE SUBMIT THE LETTER INDICATING THE PREPARENESS OF THE SITES.
		27-SEP-95	TEL	V-89	DRA RETURNED CALL FROM DR. PIERRO, DR. PIERRO ASKED WHEN NYCOMED WOULD BE DELIVERING CANDA TO THE FDA. DRA SUGGESTED 05-OCT-95, BUT THAT DATE WAS UNACCEPTABLE FOR DR. PIERRO. HE STATED THAT DELIVERY DATE OF 10 OCTOBER 1995 OR ANY DAY BETWEEN 16 OCTOBER AND 03-NOV-95 WAS ACCEPTABLE. DR. PIERRO STATED THAT HE WAS "UNOFFICIALLY" ASSIGNED AS THE MEDICAL REVIEWER.
		27-SEP-95	SUB	V-89	RESPONSE TO FDA REQUEST FOR INFORMATION DATE,

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		27-SEP-95	SUB	V-89	22-SEP-95. DRA PROVIDED CSO ALL PREVIOUS CORRESPONDENCE BETWEEN NYCOMED AND THE FDA REGARDING THE CANDA FOR TESLASCAN. ALL CANDA-RELATED SUBMISSIONS AND CONTASTS DATED FROM 21-DEC-94 TO PRESENT WERE PROVIDED.
		28-SEP-95	TEL	V-89	FDA INFORMED DRA THAT 19-OCT-95 MAY BE AN, ACCEPTABLE DATE FOR CANDA DELIVERY. DRA INQUIRED AS TO THE STATUS OF THE OFFICICAL NOTIFICATION OF THE MEDICAL REVIEWER FDA INTIMATED THAT THE LIKELIHOOD OF RECEIVING IP STATUS IS LOW WITH THE DIVISION.
		28-SEP-95	LTF	V-89	DRA INFORMED FDA (INFORMATION SYSTEMS DESIGN), THAT THE NDA WAS SUBMITTED AND ACKNOWLDEGED ON 08-SEP-95. DRA CONTACTED THE DIVISION CONCERNING THE INSTALLATION TIMING (BEFORE OR AFTER NDA FILING).
		02-OCT-95	TEL	V-89	DRA INFORMED FDA THAT A LETTER WAS SENT, TO MR. K. EDMUNDS (SYSTEMS) INDICATING THE TYPE OF COMPUTER HARDWARE WHICH WILL BE PROVIDED WITH THE CANDA. DRA INQUIRED AS TO A DELIVERY DATE FOR CANDA DELIVERY. DRA ASKED IF A MEDICAL REVIEWER WAS ASSIGNED TO THIS NDA, FDA STATED THAT DR. PIERRO WAS GOING TO BE INVOLVED. DRA INQUIRED IF RECEIPT OF THE "PAI READINESS" LETTER WOULD AFFECT FILING OF NDA.
		02-OCT-95	TEL	V-89	DR. CHOW WANTED AN EQUIVALENT SBA WRITTEN, AND SUBMITTED TO HIM UNOFFICIALLY. AFTER DISCUSSION HE WITHDREW HIS REQUEST. DR. CHOW REQUESTED THE FOLLOWING: . THE PHASE III STUDIES (BASED ON THE PROPOSED MARKET FORMULATION), PREPARE A COM[PREHENSIVE AE TABLE DIVIDED BETWEEN THE MALES AND FEMALES CATEGORIZED BY MILD, MODERATE AND SEVERE. THEN GIVE THE COMBINED ANALYSIS. . OUR TABLE APPARENTLY NOTED 48 PATIENTS OUT OF 202 WHO HAD AE'S. HE CHECKED THE RAW DATA AND COUNTED 50. PLEASE EXPLAIN THE DISCREPANCY.
		04-OCT-95	TEL	V-89	FDA INFORMED DRA THAT THE "PAI READINESS", LETTER WILL AFFECT FILING OF THE NDA. FDA STATED STANDARD REVIEW HAS BEEN DEEMED APPROPRIATE AFTER GREAT DELIBERATION. THE DIVISION FEELS OTHER MODALITIES ARE JUST AS EFFECTIVE.

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		04-OCT-95	SUB	V-89	DRA PROVIDED TO DR. DAVID, A NEW DISKETTE, CONTAINING THE CMC SUMMARY OF THE NDA.
		05-OCT-95	TEL	V-89	DRA CALLED SANFORD WILLIAMS TO ASK IF DR. PIERRO, IS "OFFICIALLY THE MEDICAL REVIEWER. MR. WILLIAMS STATED THAT DR. PIERRO WILL BE INVOLVED IN THE REVIEW. MR. WILLIAMS INDICATED THAT 19-OCT-95 CANDA DELIVERY IS FINE.
		06-OCT-95	TEL	V-89	DR. PLACE NOTIFIED DRA THAT HE HAS RECEIVED, THE DISKETTE CONTAINING THE CMC SUMMARY OF THE TESLASCAN NDA 20-652. DR. PLACE INQUIRED AS TO THE STATUS OF THE LETTER INDICATING THE MANUFACTURING SITES ARE READY FOR PREAPPROVAL INSPECTION. DRA STATED THAT A LETTER WAS CURRENTLY BEING DRAFTED.
		06-OCT-95	TEL	V-89	DRA CONTACTED THE FDA TO INFORM THEM, THE TARGET DATE FOR THE INITIATION OF THE CANDA PRESENTATION WOULD BE 1:30 PM ON 19 OCTOBER 1995. APPROXIMATE TIMES FOR THE PRESENTATION WOULD BE 1 HOUR FOR THE IMAGING CANDA AND 1 HOUR FOR THE STATISTICS COMMENTS OF CANDA. ANY QUESTIONS WOULD RESULT IN A PRESENTATION TIME OF OVER 2 HOURS. FDA INDICATED A 2-2.5 HOUR PRESENTATION AT 1:30 MAY NOT BE POSSIBLE AND REQUESTED AN EARLIER START TIME. DRA WOULD INVESTIGATE THIS OPTION AND RESPOND LATER.
		10-OCT-95	TEL	V-89	FDA REQUESTED ANOTHER COPY OF DISK NO.9, (FILE MAST2556.WP5) BECAUSE AS IT WAS LOADED INTO THE COMPUTER, IT WAS NOTED, THAT IT WAS EMPTY. FDA DISCUSSED ISSUES REGARDING TRANSFER OF THE CMC INFORMATION FROM THE DISKETTES (WP VERSION 5.2) TO (WP VERSION 6.1). THE CHEMICAL STUCTURES WERE INCOMPLETELY TRANSFERRED AS LINES ONLY, LACKING ANY ALPHABETIC/NUMERIC CHARACTERS. FDA REQUESTED THE CHEMISTRY GRAPHICS IN THEIR "NATIVE FORMAT". FDA INDICATED THAT ON THE FILES WE SENT, THE ATTRIBUTES WERE CHANGED TO "READ ONLY" TO ENSURE THE INFORMATION CAN NOT BE CHANGED BY THE REVIEWER.
		10-OCT-95	TEL	V-89	MULTIPLE DATES 10,11,12 OCT 1995:, . DRA CONFIRMED WITH FDA THAT NYCOMED IS PREPARED TO

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		10-OCT-95	TEL	V-89	CONDUCT THE CANDA DEMONSTRATION ON 19-OCT-95 AT 11:00 AM . DRA REQUESTED FDA FAX NYCOMED A COPY OF THE NDA LETTER DATED 26-SEP-95 STATING RECEIPT OF THE TESLASCAN NDA 20-652 AND S-1 REVIEW STATUS . FDA CALLED TO CONFIRM THAT DRA HAD RECEIVED THE FAX. DRA EXPLAINED TO THAT NYCOMED AND RESEARCH DATA WORLDWIDE WOULD PERFER TO BEGIN THE CANDA DEMONSTRATION AT 10:00 A.M. ON 19-OCT-95. FDA WILL CONFIRM AVAILABLITY OF CONFERENCE ROOM. FDA SUGGESTED DRA CONTACT KEN EDMUNDS REGARDING THE DELIVERY OF THE CANDA. . DRA CONTACTED FDA AGAIN AND THEY CONFIRMED THAT WE WERE SCHEDULED FOR THE CANDA DEMO AT 10:00 A.M. ON 19-OCT-95 FDA STATED THAT DR. PIERRO WOULD BE THE OFFICIAL MEDICAL REVIEWER. FDA INQUIRED AS TO THE QUANTITY AND DIMENSIONS OF THE HARDWARE COMPRISING THE IMAGING SYSTEM. DRA EXPLAINED JUST WHAT WOULDE BE DELIVERED AND FDA SAID THAT IT WOULD NOT FIT INTO THE REVIEWER'S OFFICE, BUT WOULD LOOK FOR AN APPROPRIATE SPACE. . DRA GAVE A BRIEF DESCRIPTION OF WHOM WOULD BE ATTENDING THE CANDA DEMO FROM NYCOMED. FDA STATED THAT BOTH DRS. SOBHAN AND PIERRO ARE BOTH VERY COMPUTER LITERATE AND WOULD BE ATTENDING THE DEMO. . FDA SUGGESTED THAT DRA CONTACT DR. SOBHAN REGARDING THE FORMAT FOR THE SAS DATA SETS AND CONTACT DR. SECKLER REGARDING DELIVERY OF THE CANDA EQUIPMENT.
		12-OCT-95	SUB	V-89	RESPONSE TO FDA REQUEST FOR INFORMATION, DATED 10-OCT-95. DRA PROVIDED ANOTHER COPY OF DISKETTE NO.9 CONTAINING FILE MAST2556.WP5 AND CHEMISTYRY GRAPHICS IN THEIR ORIGINAL FORMAT. THIS INFORMATION WAS SENT TO DR. DAVID PLACE.
		13-OCT-95	TEL	V-89	DRA ASKED MR. SOBHAN WHAT FORMAT HE WOULD, LIKE THE SAS DATA SETS: ON FLOPPY DISKS OR TAPE? HE WOULD PREFER THE SAS DATASETS ON DISK.
		13-OCT-95	TEL	V-89	DRA CONTACTED MR. KENNETH EDMUNDS TO DISCUSS, DELIVERY ARRANGEMENTS FOR THE MANGAFODIPIR CANDA AND IMAGING SYSTEM ON 19-OCT-95. R. BALLERINI (CLINICAL

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		13-OCT-95	TEL	V-89	RESEARCH) EXPLAINED TO THE FDA THAT THE DEMONSTRATION WOULD CONSIST OF 2 PARTS: THE CANDA DEMONSTRATION AND THE IMAGING SYSTEM DEMONSTRATION. R. BALLERINI ALSO DESCRIBED THE SIZE, COMPLEXITY AND HARDWARE FOR EACH SYSTEM AND STATED NYCOMED WOULD PREFER TO SET UP THE IMAGING SYSTEM IN A "PERMANENT" WORKING AREA. DRA EXPLAINED THE CSO SET UP A CONFERENCE ROOM FOR THE CANDA DEMONSTRATION BUT HAD NOT YET LOCATED A ROOM FOR THE IMAGING INSTALLATION. MR. EDMUNDS STATED HE WOULD CONTACT THE CSO TO GET THE ISSUE RESOLVED ASAP. MR. EDMUNDS STATED THAT SECURITY WOULD INSPECT THE EQUIPMENT WHEN IT ARRIVES AT FDA.
		16-OCT-95	TEL	V-89	MULTIPLE DATES 16, 17-OCT-95:, . DRA CONTACED FDA REGARDING AVAILABILITY OF SPACE FOR THE IMAGING SYSTEM. DRA EXPLAINED THAT NYCOMED WANTED A PERMANENT ROOM FOR THE SYSTEM. . FDA CALLED BACK TO ASK IF DRA PLANNED ON SUPPLING A TABLE . DRA CALLED FDA AND INFORMED THEM THAT NYCOMED WOULD SUPPLY A FIVE FOOT TABLE AT TIME OF DELIVERY OF CANDA. FDA STATED THE CANDA DEMONSTRATION WILL BE IN ROOM 18B-24 . DRA RETURNED FDA'S CALL IN WHICH FDA CONFIRMED READINESS FOR INSTALLATION OF THE IMAGING SYSTEM FOR THE CANDA. . DRA INFORMED FDA THAT THE LETTER INDICATING NYCOMED'S READINESS FOR PREAPPROVAL INSPECTION HAD BEEN SENT. FDA REQUESTED THAT DRA FAX A COPY OF THIS LETTER TO DR. DAVID PLACE (CHEMISTRY REVIEWER)
		17-OCT-95	LTF	V-89	DRA INFORMED FDA THAT NYCOMED COMMITS TO, BEING READY FOR INSPECTION OF ALL MANUFACTURING FACILITIES WITHIN SIX MONTHS. HOWEVER, IT IS NYCOMED'S INTENT TO BE READY 30-NOV-95. DRA ASKED FDA TO CONTACT NYCOMED IMMEDIATELY IF THE INSPECTIONS IS TO BE COMPLETED PRIOR TO THIS DATE.
		17-OCT-95	TEL	V-89	FDA WAS CONTACTED BY DRA AND CLINICAL TO,

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WIN Number: 59010
Common Drug Name: TESLASCAN
NDA Number: 20-652
NDA Description: MRI-LIVER LESIONS -INJ

Date(s): (01-JAN-55 -> 01-JAN-99)
Supplement No.(s): (0 -> XXX)
Subject: (%)
Communication Type: (%)

Supp No.	Amend No.	Date	Comm. Type	Location	Abstract
		17-OCT-95	TEL	V-89	CLARIFY THE FORMAT IN WHICH NYCOMED SHOULD SUPPLY THE SAS DATA SETS. CLINCAL EXPLAINED THAT THE SAS DATA SETS WERE TOO LARGE TO FIT ON DISKS AND THAT NYCOMED WOULD PREFER TO SUPPLY THEM WITH THE ANALYSIS DATA SETS. FDA CONFIRMED THAT IT WOULD BE ACCEPTABLE. FDA INQUIRED WHAT WAS CONTAINED ON THE LAPTOPS. CLINICAL EXPLAINED THAT THE CLINICAL CANDA, (NOT THE SAS DATA SETS) WERE ON THE LAPTOPS, BUT THE DATA SETS USED TO CONSTRUCT THE CANDA WERE CREATED ON THE MAINFRAME AND THEY ARE READABLE AS SAS DATA SETS. NYCOMED STATED THEY WILL SUPPLEY FDA WITH ALL OF THE SAS ANALYSIS DATA SETS, INCLUDING ALL OF THE AE AND EFFICACY DATA FILES.
		18-OCT-95	SUB	V-89	DRA PROVIDED 3 DISKETTES CONTAINING SUMMARY, DOCUMENTS FOR NDA 20-652.
		18-OCT-95	TEL	V-89	FDA CALLED TO REQUEST NYCOMED TO BRING, WHEN THE CANDA IS DELIVERED (19 OCT), TWO DESK COPIES OF VOLUME 1.1 OF THE NDA. FDA ALSO STATED THE ROOM OBTAINED FOR THE IMAGING SYSTEM IS EMPTY AND THAT NYCOMED SHOULD STILL SUPPLY THE FIVE FOOT LONG TABLE FOR THE IMAGING SYSTEM.
		23-OCT-95	SUB	V-89	DRA PROVIDED DR. MAHBOOB SOBHAN (CSO) THE, SAS DATA SETS WHICH WERE SUPPLIED TO HIM 19-OCT-95 AT THE CANDA DEMONSTRATION. THIS DISK CONTAINS THE FORMATS CATALOG TRANSPORT FILE.
		24-OCT-95	TEL	V-89	DRA AND FDA DISCUSSED THE FOLLOWING:, . DRA CALLED REGARDING THE PAI READINESS LETTER WHICH WAS SENT TO NDA 20-652 ON 18-OCT-95, THE 45-DAY CHECKLIST, AND THE FILABILITY ISSUE . FDA STATED THAT NYCOMED "MUST" COMMIT TO A PAI-READINESS DATE. DRA REITERATED THE STATEMENT WHICH WAS IN THE 18TH OCT LETTER FOR PAI-READINESS ON 30 NOV. FDA STATED THE WORDING IN THAT LETTER WAS VAGUE. DRA AGAIN EXPLAINED THAT 30 NOV DATE WAS NOT A ISSUE FOR NYCOMED. DRA WILL SUBMIT ANOTHER LETTER STATING NYCOMED'S COMMITTMENT . DRA INFORMED FDA THAT A COPY OF THE "NEW" PAI-READINESS LETTER AND A COPY OF THE 45-DAY CHECKLIST HAD BEEN SENT.

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		24-OCT-95	TEL	V-89	. FDA EXPLAINED THAT SINCE INITIATION OF THE USER FEE ACT, THE FDA'S TIMELINES HAVE BECOME MUCH TIGHTER TO RENDER DECISIONS; THIS IS THE RATIONALE FOR THE PAI READINESS REQUIREMENT OF NO LONGER THAN 4 MONTH. (THIS BECAME A LENGTHLY DISCUSSION) . DRA ASKED IF NYCOMED COULD OBTAIN THE CHECKLIST BEING USED TO DETERMINE FILABILITY OF THE NDA. FDA RESPONDED THAT THE CHECKLISTS ARE NOT OFFICIAL DOCUMENTS AND THAT MANY CIRCULATE WITHIN THE AGENCY. . FDA CALLED TO POINT OUT DIFFERENCES BETWEEN THEIR CHECKLIST AND THE ONE NYCOMED FAXED EARLIER. THE ONLY DIFFERENCES DEALT WITH PAI-READINESS.
		24-OCT-95	OTH	V-89	ADDENDUM TO CONTACT REPORT DATED 24-OCT-95, REGARDING THE FIRST SENTENCE OF THE FIRST PARAGRAPH OF THE SUMMARY THE PAI READINESS LETTER WAS ACTUALLY DATED 17-OCT-95. THE DATE WAS INADVERTENTLY INDICATED AS 18-OCT-95
		24-OCT-95	LTF	V-89	DRA INFORMED FDA THAT AS INDICATED IN OUR, LETTER DATED 18-OCT-95, AND IN ACCORDANCE WITH THE 45-DAY CHECKLIST ISSUED BY THE FDA FREEDOM OF INFORMATION OFFICE, NYCOMED COMPLIED WITH THE GUIDANCE OF READINESS FOR INSPECTION WITHIN SIX MONTHS FOR A 1-S COMPOUND. DRA STATED THERE SEEMS TO BE DIFFERENT RULES IN EACH DIVISION REGARDING PAI READINESS AS A FILING ISSUE, BECAUSE THE REGULATIONS DO NOT IDENTIFY THIS AS A BASIS TO REFUSE TO FILE. DRA REQUESTED CLARIFICATION ON THIS POINT.
		24-OCT-95	OTH	V-89	ADDENDUM TO SUBMISSION LETTER DATED 24-OCT-95, REGARDING THE SECOND SENTENCE OF THE FIRST PARAGRAPH, THE PAI READINESS LETTER WAS INADVERTENTLY REFERENCED AS DATED 18-OCT-95. IT WAS ACTUALLY DATED 17-OCT-95
		27-OCT-95	TEL	V-89	MULTIPLE DATES: 27 AND 30-OCT-95, 27-OCT-95: . FDA CONTACTED DRA TO DETERMINE WHETHER NDA 20-652

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		27-OCT-95	TEL	V-89	CONTAINS THE FOLLOWING STATEMENTS 1) NONCLINICAL STUDIES COMPLY WITH 21 CFR 58.0 2) CLINICAL STUDIES COMPLY WITH IRB AND/OR DECLARATION OF HELSINKI. 30-OCT-95: . DRA CONTACTED FDA TO ADDRESS THE QUESTIONS POSED 27-OCT 1) THERE IS NOT A STATEMENT REGARDING NONCLINICAL STUDIES BEING CONDUCTED IN COMPLIANCE WITH GLP DUE TO IT NOT BEING A REQUIREMENT FOR ALL NONCLINICAL STUDIES. DRA WILL FAX TO FDA A LIST OF PRECLINICAL STUDIES AND INDICATE WHICH WERE CONDUCTED IN ACCORDANCE WITH GLP. 2) DRA STAED IN EACH U.S. PROTOCOL THERE IS A STATEMENT VERIFYING CONDUCT UNDER IRB APPROVAL. DRA QUESTIONED IF FDA STILL REQUIRES A SINGLE STATEMENT (INCLUDING ALL OF THE STUDIES) TO THIS EFFECT. DRA MENTIONED THERE WAS ONE STUDY CONDUCTED OVERSEAS AND WAS CONDUCTED ACCORDING TO GERMAN MEDICATIONS LAW REGULATIONS. DRA IS IN PROCESS OF VERIFYING IF THAT STUDY WAS ALSO CONDUCTED UNDER THE DECLARATION OF HELSINKI. FDA REMINDED DRA OF DR. PIERRO'S REQUEST FOR A DISKETTE CONTAINING MICROSOFT EXCEL VERSION 3.1 FOR HIS CANDA LAPTOP.
		31-OCT-95	FAC	V-89	RESPONSE TO TELEPHONE CONTACTS 27,30-OCT-95, DRA PROVIDED FDA WITH A COPY OF SECTION 5.4 (TOXICOLOGY) OF NDA 20-652. SECTION 5.4 INCLUDES THE OVERALL INDEX OF TOXICOLOGY STUDIES AND SPECIFIC STUDIES WHICH COMPLY WITH GOOD LABORATORY PRACTICES. DRA EXPLAINED THERE ARE SOME NONCLINICAL STUDIES INCLUDED IN THE NDA THAT WERE NOT REQUIRED TO BE CONDUCTED UNDER 21 CFR 58.0 AND THAT AN OVERALL STATEMENT INDICATING COMPLIANCE OF NONCLINICAL STUDIES IS NOT APPROPRIATE. NYCOMED IS WAITING FOR CLARIFICATION REGARDING THE STATEMENT FOR CLINICAL STUDIES.
		01-NOV-95	TEL	V-89	FDA STATED DISK CONTAINING THE SAS FORMATS, CATALOG TRANSPORT FILE WAS RECEIVED, BUT FDA IS UNCLEAR HOW TO USE IT. NYCOMED BIOSTATS INDIVIDUAL EXPLAINED HOW TO USE THE DISK TO ACCESS THE SAS DATA SETS.

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		01-NOV-95	SUB	V-89	RESPONSE TO FDA REQUEST FOR INFORMATION, DATED 27-OCT-95. DRA PROVIDED A COPY OF SECTION 5.4 (TOXICOLOGY) OF NDA 20-652 WHICH INCLUDES THE OVERALL INDEX OF TOXICOLOGY STUDIES, AS WELL AS THOSE SPECIFIC STUDIES WHICH COMPLY TO THE GOOD LABORATORY PRACTICES, 21CFR 58.0. THIS INFORMATION WAS FAXED TO MR. SANFORD WILLIAMS ON 31-OCT-95.
		02-NOV-95	TEL	V-89	FDA WAS NOTIFIED THAT PREMIER RESEARCH, WORLDWIDE OBTAINED THE MIRCOSOFT EXCEL PROGRAM AND DELIVERY TO THE FDA WAS SET FOR 03 NOVEMBER 1995.
		02-NOV-95	TEL	V-89	FDA INDICATED NDA 20-652 IS "FILABLE", AND THAT THERE ARE SOME ISSUES TO WHICH NYCOMED MUST RESPOND NO ADDITONAL INFORMATION WILL BE GIVEN UNTIL SOME RESEARCH HAS BEEN CONDUCTED. NYCOMED'S RESPONSE REGARDING PRECLINICAL AND CLINICAL STUDY COMPLIANCE WILL NOT HAVE ANY IMPACT ON NDA 20-652.
		03-NOV-95	TEL	V-89	DRA WAS NOTIFIED THAT MICROSOFT EXCEL HAS, BEEN LOADED ONTO THE LAPTOPS OF THE MEDICAL REVIEWERS AND THEY ARE IMPRESSED BY THE COMPUTER PACKAGE. IT WAS MENTIONED THAT DR. CHOW WILL BE CONDUCTING THE SAFETY REVIEW AND THE REVIEW WOULD BE EASIER IF HE ALSO HAD A LAPTOP.
		06-NOV-95	TEL	V-89	06,07-NOV-95, FDA INDICATED THE NDA, WOULD BE FILED 14-NOV-95. DRA INQUIRED AS TO A LETTER TO ACKNOWLEDGE FILING. FDA LATER RESPONDED ONLY "REFUSAL TO FILE" LETTERS ARE SENT.
		09-NOV-95	TEL	V-89	DR. CHOW REQUESTS A LAP-TOP COMPUTER FOR HIS, REVIEW OF NDA 20-652. DRA INDICATED THE MATTER WOULD BE DISCUSSED WITH THE APPROPRIATE INDIVIDUALS.
		13-NOV-95	TEL	V-89	MULTIPLE DATES 13,14-NOV-95 RE: PK STUDY, 13-NOV-95 . FDA CALLED TO ARRANGE A TELECONFERENCE BETWEEN THE BIOPHARMACEUTICS REVIEWER, CSO AND NYCOMED PERSONNEL. THE BIOPHARMACEUTICS REVIEWER IS REQUESTING INFORMATION

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		13-NOV-95	TEL	V-89	ON THE STATUS OF THE 59010-008 PK STUDY. . DRA MENTIONED A CONVERSATION WITH DR. CHOW REGARDING THE ISSUE OF A LAP-TOP FOR HIS REVIEW OF NDA 20-652 AND THAT THE ISSUE IS UNDER CONSIDERATION. 14-NOV-95 . FDA CONFIRMED 1:00PM ON 15-NOV-95 WOULD BE ACCEPTABLE FOR THE TELECONFERENCE.
		14-NOV-95	TEL	V-89	MULTIPLE CONTACTS 14,15-NOV-95, . FDA CONFIRMED TIME AND TELEPHONE NUMBER FOR THE TELECONFERENCE AT 1:00 PM, 15-NOV-95 TO DISCUSS THE PHARMACOKINETIC STUDY. . MR. EDMUNDS REQUESTED A LETTER FROM NYCOMED AUTHORIZING . PREMIER RESEARCH WORLDWIDE TO TRANSFER THE CANDA INFORMATION FROM THE LAPTOPS TO THE DESKTOP COMPUTERS OF THE MEDICAL REVIEWERS, THE LETTER SHOULD ALSO BE SUBMITTED. . DRA INFORMED THE FDA THAT DUE TO BUGETARY CONSTRAINTS, NYCOMED COULD NOT SUPPLY DR. CHOW WITH A LAPTOP CONTAINING THE CANDA.
		15-NOV-95	FAC	V-89	RESPONSE TO REQUEST MADE 14 NOVEMBER 1995, A LETTER AUTHORIZING PREMIER RESEARCH WORDWIDE TO TRANSFER CANDA INFORMATION FROM LAPTOPS TO THE DESKTOP COMPUTERS OF THE MEDICAL REVIEWERS.
		15-NOV-95	LTF	V-89	DRA PROVIDED A COPY OF THE LETTER WHICH, WAS SENT TO MR. KENNETH EDMUNDS, 15-NOV-95, AUTHORIZING PREMIER RESEARCH WORLDWIDE (FORMERLY RESEARCH DATA WORLDWIDE) TO TRANSFER THE TESLASCAN CANDA INFORMATION CONTAINED ON THE TWO DELL LAPTOP COMPUTER (DELIVERED TO FDA ON 19-OCT-95) TO THE DESKTOP COMPUTERS OF THE MEDICAL REVIEWERS.
		15-NOV-95	TEL	V-89	TELECONFERENCE-STATUS OF PROTOCOL 59010-008, THE CURSORY REVIEW OF THE HUMAN PHARMACOKINETICS SECTION OF THE NDA WAS PERFORMED;IT WAS NOTED NYCOMED SUBMITTED ONLY 2 HUMAN PK STUDIES. FDA ASKED NYCOMED TO PROVIDE INFORMATION ON PROTEIN BINDING; DRUG INTERACTIONS AND DESCRIBE THE METABOLIC FATE OF THE ENTIRE DRUG PRODUCT.

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		15-NOV-95	TEL	V-89	. NYCOMED INDICATED STUDIES REGARDING THE PROTEIN BINDING ISSUE WERE BEING CONDUCTED. . ALSO INDICATED WAS THAT INFORMATION REGARDING DRUG INTERACTIONS AND CONCOMITANT MEDICATIONS WAS NOT SPECIFICALLY DISCUSSED IN THE PK SECTION OF THE NDA BUT WAS ADDRESSED IN THE INTEGRATED SUMMARY OF SAFETY. FDA INDICATED THAT THE REVIEW OF THE STUDY REPORT FOR PROTOCOL 59010-008 WAS EXTREMELY IMPORTANT DUE TO THE STUDY BEING CONDUCTED ON HEPATICALLY IMPAIRED PATIENTS. FDA WAS ASKED WHEN THE REVIEW WOULD BEGIN BUT DECLINED TO OFFER A DATE. FDA ASKED OF THE REVIEW STATUS OF THE PK STUDY. NYCOMED DESCRIBED THE KEY EVENTSTO BE COMPLETED PRIOR TO SUBMITTING THE FINAL REPORT AND GAVE THE CURRENT PROJECTED TIME AS MID-APRIL. FDA ASKED IF THE TIME LINE COULD BE ACCELERATED. NYCOMED RESPONDED THAT DEPARTMENTAL MANAGEMENT WOULD BE CONSULTED. FDA REQUESTED NYCOMED FAX THEM AN OUTLINE OF THE TIME LINES WHEN THEY ARE ESTABLISHED.
		15-NOV-95	TEL	V-89	FDA WILL BE FAXING A COPY OF THE MINUTES, PREPARED BY NYCOMED AND PREPARED BY THE DIVISON, FROM THE PRE-NDA MEETING HELD 29-NOV-94. DRA LATER CONFIRMED RECEIPT OF THE FAX. DRA ALSO INFORMED THE CSO OF A FAX SENT TO KEN EDMUNDS AUTHORIZING RDW TO TRANSFER DATA FILES FROM CANDA TO THE DESK TOP COMPUTERS OF THE MEDICAL REVIEWERS. DRA ASKED THE CSO TO DISTRIBUTE THE FAX TO THE MEDICAL REVIEWERS. IT WAS REQUESTED THE AUTHORIZATION LETTER BE FORMALLY SUBMITTED TO THE NDA.
		15-NOV-95	FAC	V-89	DRA FAXED MR. SANFORD WILLIAMS A COPY OF THE, LETTER THAT WAS FAXED TO MR. KENNETH WILLIAMS WHICH AUTHORIZES PREMIER RESEARCH WORLDWIDE TO TRANSFER THE CANDA INFORMATION TO THE DESKTOP COMPUTERS OF THE MEDICAL REVIEWERS. HE WAS ASKED TO DISTRIBUTE THIS LETTER TO DRS. PIERRO AND CHOW.
		05-DEC-95	TEL	V-89	OFFICE OF COMPLIANCE REQUESTED THE, FOLLOWING INFORMATION: . LIST OF ALL ADEQUATE AND WELL CONTROLLED TRIALS SUBMITTED

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		05-DEC-95	TEL	V-89	IN THE NDA. . COPIES OF EACH OF THE CLINICAL PROTOCOLS. . LIST OF THE NAMES AND ADDRESSES OF ALL INVESTIGATORS. . LIST OF ENROLLED SUBJECTS FOR EACH INVESTIGATOR.
		08-DEC-95	SUB	V.90-91	RESPONSE TO FDA REQUEST FOR INFORMATION, DATED 05-DEC-95. DRA PROVIDED MR. ROBERT YOUNG (OFFICE OF COMPLIANCE) WITH THE FOLLOWING INFORMATION: . LIST OF ALL ADEQUATE AND WELL-CONTROLLED TRIALS . COPIES OF ALL CLINICAL PROTOCOLS . LIST OF NAMES AND ADDRESSES OF ALL INVESTIGATORS AND LIST OF TOTAL ENROLLED SUBJECTS FOR EACH INVESTIGATOR
		12-DEC-95	TEL	V-92	FDA CALLED TO CLARIFY THE LOCATION, OF 3 TABLES WHICH ARE REFERENCED IN VOLUME 1.0, PAGE 44, SECTION 5.1.2 OF NDA 20-652. DRA INDICATED THAT THE TABLES ARE FOUND IN THE "TABLES OF ALL STUDIES" LISTED IN VOLUME 1.11, PAGES 16-14. FDA REQUESTED A COPY OF THE TABLES BE SENT TO THEM.
		12-DEC-95	TEL	V-92	OFFICE OF COMPLIANCE CALLED AND INDICATED, THE INFORMATON REQUESTED FROM NYCOMED WAS RECEIVED. A REQUEST WAS MADE FOR THE FOLLOWING INFORMATION: . CASE REPORT FORMS FOR SUBJECTS 001, 020, 040 AND 060 ENROLLED IN PROTOCOL 59010-001 . CASE REPORT FORMS FOR SUBJECTS 001, 007, 014, AND 021 ENROLLED IN PROTOCOL 59010-003. . COPY OF FORM FDA 1572 AND CURRICULUM VITAES FOR INVESTIGATORS THAT ARE CONDUCTING THE ABOVE PROTOCLS. . THE NUMBER OF PATIENS ENROLLED BY BOTH INVESTIGATORS, HOW MANY OF THE ENROLLED PATIENTS WERE EVALUABLE, AND HOW MANY WERE NOT EVALUABLE, BROKEN DOWN BY THE INVESTIGATOR. . ADVERSE EVENTS LISTING FOR EACH OF THE ABOVE INVESTIGATORS.
		12-DEC-95	SUB	V-92	RESPONSE TO FDA REQUESTED DATED 12-DEC-95, DRA PROVIDED A WORDFERFECT DISKETTE, VERSION 6.0/6.1 CONTAINING THE DRAFT PACKAGE LABELING IN COLUMN FORMAT, AND

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		12-DEC-95	SUB	V-92	THE "TABLE OF ALL STUDIES" CONTAINED IN VOLUME 1.11 OF NDA 20-652
		14-DEC-95	TEL	V-94	MULTIPLE DATES; 14,15-DEC-95, 14-DEC-95: FDA INQUIRED AS TO THE CURRENT TIMELINES FOR SUBMITTING THE REPORT FOR CLINICAL PROTOCOL 59010-2-008. DRA INDICATED THE CURRENT TIMELINES WERE MID-END OF MARCH FOR SUBMISSION OF THE FINAL REPORT BUT WOULD CHECK WITH CLINICAL STAFF FOR A DEFINITE DATE. 15-DEC-95: FOLLOW-UP ON 59010-2-008 TIMELINES. DRA STATED THE DATE FOR SUBMISSION COULD BE NARROWED TO THE LAST TWO WEEKS IN MARCH 1996.
		14-DEC-95	SUB	V-93	RESPONSE TO FDA REQUEST FOR INFORMATION DATE, 12-DEC-95. DRA PROVIDED THE FOLLOWING INFORMATION: . CASE REPORT FORMS FOR SUBJECTS 001, 020, 040, AND 060 ENROLLED IN PROTOCOL 59010-001 . CASE REPORT FORMS FOR SUBJECTS 001, 007, 014, AND 021 ENROLLED IN PROTOCOL 59010-003 . COPY OF FORM FDA 1572 AND CURRICULUM VITAE FOR DRS. FEDERLE AND HARMON . THE NUMBER OF PATIENTS ENROLLED AND THE TOTAL NUMBER OF EVALUABLE PATIENTS FOR DRS. FEDERLE AND HARMON . ADVERSE EVENT LISTINGS FOR DRS. FEDERLE AND HARMON
		14-DEC-95	TEL	V-94	MULTIPLE DATES; 14,15-DEC-95, 14-DEC-95: FDA INQURIED AS TO WHETHER ANY OF THE CLINICAL STUDY PROTOCOLS AND THE PHASE II STUDY CONDUCTED IN GERMANY (BYK GULDEN) WERE FURNISHED WITH THE NDA IN ELECTRONIC FORMAT. DRA INDICATED NOT ALL ITEMS WERE AVAILABLE IN ELECTRONIC FORMAT. FDA STATED IT WOULD HELP WITH THE REVIEW. DRA WOULD LOOK INTO PROVIDING THE NEEDED INFORMATION IN ELECTRONIC FORMAT. FDA ASKED IF NYCOMED PROVIDED A SUMMARY OF THE PUBLISHED CLINICAL REFERENCES. DRA STATED A SUMMARY WAS NOT PROVIDED. FDA ASKED IF ANY OF THE REFERENCES WERE CRITICAL TO THE

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		14-DEC-95	TEL	V-94	APPROVAL. DRA WAS NOT AWARE OF ANY CRITICAL REFERNCES BUT WOULD CONFIRM WITH THE CLINICAL DEPARTMENT. 15-DEC-95: FOLLOW UP TO 14-DEC-95. DRA INDICATED NYCOMED WOULD PROVIDE FDA WITH A DISKETTE CONTAINING AN ELECTRONIC VERSION OF CLINICAL PROTOCOLS 59010-2-001,002,003,004,005, AND 006. DRA ALSO INDICATED THERE ARE NOT ANY PUBLISHED LITERATURE REFERENCES THAT ARE CRITICAL TO THE APPROVAL OF THE NDA.
		18-DEC-95	SUB	V-94	RESPONSE TO FDA REQUEST DATED 14-DEC-95, DRA PROVIDED A DISKETTE CONTAINING COPIES OF THE FOLLOWING CLINICAL PROTOCOLS: 59010-2-001, 59010-2-002, 59010-2-003, 59010-2-004, 59010-2-005, AND 5910-2-006
		03-JAN-96	TEL	V-94	SANTFORD WILLIAMS (CSO) CALLED AND REQUESTED, A PERSONAL DESK COPY OF THE TESLASCAN INTEGRATED SUMMARY OF SAFETY. HE ALSO INDICATED THAT IN HIS REVIEW OF VOL 1 OF THE NDA HE WAS UNABLE TO LOCATED WHERE WE REQUESTED EXCLUSIVITY. HE ASKED IF WE WERE GOING TO SEND A LETTER REQUESTING EXCLUSIVITY. DRA STATED WE WOULD GET BACK TO HIM.
		04-JAN-96	TEL	V-94	DRA CONTACTED THE FDA IN AN ATTEMPT, TO CLARIFY THE FDA'S REQUEST FOR A STATEMENT OF EXCLUSIVITY FOR THE NDA. DRA WAS ABLE TO FIND A NEW REGULATION, 21 CFR 314.50 (J), WHICH DEALS WITH EXCLUSIVITY. FDA INDICATED THAT THIS DID NOT ADDRESS THE ISSUE TO WHICH THEY WERE REFERRING. FDA INDICATED THEY WANT A STATEMENT OF EXCLUSIVITY WITH THE PATIENT INFORMATION WHICH APPEARS IN THE NDA. FDA ALSO INDICATED THAT NYCOMED IS NOT REQUIRED TO PROVIDE THE STATEMENT OF EXCLUSIVITY, BUT SUGGESTED IT WOULD BE TO NYCOMED'S ADVANTAGE. FDA INDICATED THE STATEMENT IS NOT USUALLY AN ISSUE UNTIL LATER IN THE REVIEW PROCESS. DRA WILL CONVEY THE INFORMATION TO MANAGEMENT.
		05-JAN-96	SUB	V-94	RESPONSE TO FDA REQUEST FOR INFORMATION, DATED 03-JAN-96. DRA PROVIDED THE INTEGRATED SAFETY SUMMARY FOR TESLASCAN WHICH CONSISTS OF VOLUMES 1.85 AND 1.86 OF THE NDA.

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		16-JAN-96	SUB	V-95	DRA PROVIDED THE FOUR-MONTH SAFETY UPDATE, WHICH INCLUDES REVISIONS TO NDA STABILITY DATA TABLES.
		16-JAN-96	TEL	V-96	MULTIPLE DATES; 16,17-JAN-96, 16-JAN-96: DRA CONTACTED FDA TO FOLLOW UP ON THE PROBLEM OF EXPORTING "DISCOMFORT" DATA TO EXCEL. FDA INDICATED THE PROBLEM WAS WITH FORMATTING AND MANIPULATION OF THE DATA ONCE IT WAS EXPORTED. 17-JAN-96: CLINICAL SPOKE WITH FDA TO DETERMINE THE CAUSE OF THE FORMATTING PROBLEM. CLINICAL WILL CHANGE THE DATA FORMAT AND PROVIDE PREMIER RESEARCH WORLDWIDE WITH THE NEW DATA FORMAT TO BE LOADED ONTO THE CANDA FOR FDA.
		16-JAN-96	TEL	V-96	FDA CONTACTED DRA TO REQUEST ASSISTANCE, MANIPULATING THE PHASE 3 INJECTION-ASSOCIATED DISCOMFORT DATA. FDA INDICATED THE REVIEW WILL CONSIDER ONLY THE PHASE 3 CLINICAL TRIALS AS PIVOTAL STUDIES SINCE THEY UTILIZE THE NEW FORMULATION. FDA IS ATTEMPTING TO EXPORT INJECTION-ASSOCIATED DISCOMFORT DATA CONTAINED IN THE CANDA TO AN EXCEL SPREADSHEET. FDA THEN INTENDS TO APPLY ADDITIONAL STATISTICS TO THE DATA AND CREATE A TABLE SIMILAR TO THE ONE FOUND IN NDA VOL 60 PAGE 65 OF 116. DRA WILL FOLLOW-UP WITH NYCOMED'S STATISTICIAN.
		19-JAN-96	TEL	V-96	FDA CONTACTED DRA TO REQUEST THREE DESK, COPIES OF THE FOUR MONTH SAFETY UPDATE.
		19-JAN-96	TEL	V-96	FDA REQUESTED A DISKETTE CONTAINING, LABORATORY VALUES AND VITAL SIGNS FOUND IN THE PHASE 3 CLINCIAL STUDY REPORTS APPENDICES. THESE APPENDICES WERE NOT INCLUDED IN THE CANDA.
		23-JAN-96	TEL	V-96	FDA CALLED TO INQUIRE THE STATUS OF THE, HUMAN PK STUDY (59010-2-008). DRA STATED THE DATA WAS CURRENTLY BEING ANALYZED AND THE CLINICAL STAFF WOULD START THE CLINICAL STUDY REPORT SHORTLY. FDA STATED NYCOMED SHOULD CONTACT THE BIOPHARMACEUTICS REVIEWER DIRECTLY IF NYCOMED

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		23-JAN-96	TEL	V-96	COULD PROVIDE ANY INFORMATION REGARDING THE STUDY PRIOR TO THE MID-END MARCH DEADLINE.
		23-JAN-96	SUB	V-96	RESPONSE TO FDA REQUEST FOR INFORMATION, DATED 19-JAN-96. DRA PROVIDED 3 DESK COPIES OF THE TESLASCAN FOUR MONTH SAFETY UPDATE, SUBMITTED 16-JAN-96)
		23-JAN-96	SUB	V-96	RESPONSE TO FDA REQUEST FOR INFORMATION DATE, 19-JAN-96. DRA PROVIDED DR. PIERRO WITH A WORLDPERFECT 6.0/6.1 DISKETTE CONTAING LABORATORY VALUES AND VITAL SIGNS FOUND IN THE PHASE 3 CLINICAL STUDY REPORT APPENDICES. THESE APPENDICES WERE NOT INCLUDED IN THE CANDA.
		25-JAN-96	TEL	V-96	DR. PIERRO CALLED TO SAY THAT THE DISKETTE, THAT DRA SENT ON 22-JAN-96 WAS UNREADABLE IN THE FORMAT PROVIDED. CLINICAL STATED THAT THEY WOULD REFORMAT THE DATA AND PROVIDE IT ON A NEW DISK.
		29-JAN-96	SUB	V-96	RESPONSE TO FDA REQUEST FOR INFORMATION DATE, 25-JAN-96. DRA PROVIDED DR. JOSEPH PIERRO WITH A WORDPERFECT 6.0/6.1 DISKETTE CONTAING LABORATORY VALUES, VITAL SIGNS, AS WELL AS SUMMARY STATISTICS OF THE DATA.
		01-FEB-96	TEL	V-96	DR. PIERRO CALLED TO INDICATE THAT THE, WORDPERFECT DISKETTE WHICH WAS SENT ON 25-JAN-96 WAS PROBLEMATIC TO READ. DRA STATED THEY WOULD FOLLOW-UP ON THIS PROBLEM.
		09-FEB-96	OFC	V-96	FRIDAY, 09-FEB-96 AT 9:30 AM, JOHN FALLONE WAS PRESENTED WITH AN FDA FORM 492 NOTICE OF INSPECTION. THE INVESTIGATOR REPRESENTING THE FDA IS NANCY SAXENIAN (BADGE 22034). THE PURPOSE OF THE VISIT WOULD BE TO CONDUCT AN PRE-APPROVAL INSPECTION OF MANGAFODIPIR. FDA REQUESTED A SYNOPSIS OF THE HISTORY OF BUSINESS FOR NYCOMED INC. MR. FALLONE OUTLINED THE U.S. MANUFACTURING AND CORPORATE OPERATIONS. A COPY OF THE CMC SECTION OF THE NDA HAD NOT BEEN RECEIVED BY THE INVESTIGATOR, ONE WILL BE SUPPLIED FROM TARC. THE MAJORITY OF THE DAY WAS SPENT IN ORIENTATION DISCUSSIONS

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		09-FEB-96	OFC	V-96	OF THE EQUIPMENT AND PROCESSES USED TO MANUFACTURE MANGAFODIPIR. IT WAS EXPLAINED THERE WERE TWO MANUFACTURING CAMPAIGNS IN 1993 AND 1995. THE BATCHES OF DRUG SUBSTANCE MANUFACTURED IN EACH RUN WERE IDENTIFIED.
		10-FEB-96	OFC	V-96	FDA PRE-APPROVAL INSPECTION DAY 2, THE INSPECTOR ARRIVED AT APPROXIMATELY 8:55 AM. IT WAS SUGGESTED THAT A DISCUSSION, BY DR. THIELKING, OF THE SECTIONS OF THE NDA THAT SPECIFIED THE MANUFACTURING OF THE BULK DRUG SUBSTANCE WOULD BE BENEFICIAL. THE PROCESS FLOW CHART WAS REVIEWED THEN EXPLAINED THE SPECIFIC PROCESS DESCRIPTION STARTING ON PAGE 72 OF THE NDA. THE INSPECTOR ASKED TO SEE THE IN-PROCESS TESTING MONOGRAPHS AND THE RESULTS OF MICRO TESTING FOR EACH BATCH MANUFACTURED AT THE PLANT AND ADDITIONAL INFORMATION ON BATCH 1003RW2. THE DATA WAS REVIEWED AND DISCUSSED WHY THE BATCH WAS SET ASIDE. THE AFTERNOON WAS DEVOTED TO BUILDING 2 AND THE INITIATED UPGRADE OF THE FINISHING AREA. THE DRAWING FOR THE PLANNED UPGRADE OF THE FINISHING AREA WAS REVIEWED (ROBIN CAIRNS, DR. THIELKING AND PHIL ALLAWAY PARTICIPATED). A TOUR OF THE FACILITY WAS GIVEN. IT WAS EXPLAINED THAT SOME ORIGINAL EQUIPMENT WAS NO LONGER AVAILABLE DUE TO REPLACEMENT OR THE UPGRADE. MS. SAXENIAN ASKED TO SEE THE DRYERS. IT WAS EXPLAINED HOW WE PLANNED TO UPGRADE THAT AREA. MS. SAXENIAN ASKED HOW THE PRODUCTS WOULD BE TRANSPORTED THROUGH TO THE AIR DRYER ROOM TO REDUCE THE POTENTIAL FOR CROSS CONTAMINATION. SHE WAS ASSURED THAT APPROPIATE PROCEDURES WOULD BE WRITTEN TO GOVERN THE FLOW OF THE MATERIAL. MS. SAXENIAN SEEMED SATISFIED AND AGREED THE UPGRADE WAS SIGNIFICANT.
		11-FEB-96	OFC	V-96	FDA PRE-APPROVAL INSPECTION DAY 3, THE INVESTIGATOR ARRIVED AT THE PLANT AT APPROXIMATELY 8:30 AM. UNEVENTFUL DAY, MOSTLY INFORMATION GATHERING. MS. SAXENIAN ASKED IF TARC HAD AGREED WITH THE ANALYTICAL RESULTS OBTAINED HERE. THE CONCERN WAS THAT THE RESULTS PRESENTED WITH THE NDA WERE OBTAINED BY TARC AND NOT THE MANUFACTURING

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		11-FEB-96	OFC	V-96	SITE. A COMPARISON TABLE WAS OFFERED FOR REVIEW. THE INVESTIAGTOR ASKED IF A FINISHED PRODUCT WAS ON THE PREMISES. IT WAS EXPLAINED THAT BATCH 1001N WAS RETURNED FOR EXPERIMENTAL WORK. MS. SAXENIAN ASKED TO SEE A FAILURE INVESTIGATION REPORT FOR BATCH 1003K (REWORKED TWICE FOR MICROBIAL PROBLEMS). A FAILURE INVESTIGATION REPORT HAD NOT BEEN PREPARED AND TWO DEVELOPMENT REPORTS WHERE THE FAILURE WAS DISCUSSED WERE GIVEN FOR HER REVIEW. THE INVESTIGATOR ASKED IF ANY WORK HAD BEEN DONE TO IDENTIFY THE CAUSE OF THE FUNGAL SPORE. A CHECK WITH TARC INDICATED NO ADDITIONAL WORK HAD BEEN DONE SINCE IT WAS A RANDOM OCCURANCE. MS. SAXENIAN SEEMED SATISFIED.
		12-FEB-96	OFC	V-96	FDA PRE-APPROVAL INSPECTION DAY 4, MS. SAXENIAN ARRIVED AT THE PLANT AT APPROXIMATELY 8:25 AM. THE FIRST REQUEST WAS TO SEE THE VALIDATION PLAN THAT HAD BEEN PREPARED FOR THE COMMERICAL PRODUCTION OF MANGAFODIPIR. THE SECOND REQUEST WAS TO REVIEW THE ANALYTICAL COMPARISON TABLES TAHT WE ARE PREPARING TO DEMONSTRATE INTER LAB CORRELATION OF RESULTS FOR THE RELEASE TESTING OF DRUG SUBSTANCE. MS. SAXENIAN INDICATED HER PLAN WAS TO REVIEW THE STABILITY RESULTS DUE TO HER CONCERN THAT RENSSELAER HAD NOT GENERATED THE STABILITY RESULTS THAT APPEAR IN THE REGISTRATION. IT WAS EXPLAINED TO HER THAT THE OFFICIAL TECHNOLOGY TRANSFER WAS NOT COMPLETED UNTIL JUNE 1995, PRIOR TO THAT RESULTS REPORTED WERE OBTAINED BY SWPRD OR TARC. THERE WAS A REVIEW OF THE RENSSELAER DATA FOR EACH OF THE DRUG SUBSTANCE BATCHES 1001K, 1002K, 1001N. A COMPARISON OF INTER LAB ANALYTICAL DATA WAS GIVEN AND THE PROCESS USED IN THE TRANSFER OF ANALYTICAL METHODS WAS EXPLAINED. MS. SAXENIAN STATED NO OTHER OBSERVATIONS WOULD RESULT IN A 483 AND SHE WILL RETURN ON TUESDAY 20-FEB-96. MS. SAXENIAN REQUESTED AND RECEIVED COPIES OF: 1. STABILITY TABLES FOR 1001K,1002K,1001N. ADDITIONAL DATA FOR ACCELERATED RUN AFTER JUNE 1995. 2. MEMO RIVERS: BUBOIS DATED 3-10-96; WIN 59010-2 DRUG SUBSTANCE PACKAGING. 3. SOP QC 124.5 STABILITY

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		12-FEB-96	OFC	V-96	4. COMPARISON OF ANALYTICAL RESULTS FOR BATCHES 1001K, 1002K, 1001N
		13-FEB-96	OFC	V-96	FDA PRE-APPROVAL INSPECTION DAY 5, MS. SAXENIAN ARRIVED AT THE PLANT AT APPROXIMATELY 9:30 AM. SHE REQUESTED TO SPEAK WITH JOHN FALLONE AND PATRICIA ELLIS THE INSPECTION HAD TAKEN A TURN OF DIRECTION. MS. SAXENIAN EXPLAINED SHE WAS ENDING THE INSPECTION AFTER DISCUSSIONS WITH THE FIELD OFFICE. THE FDA POSITION WAS THAT THEY COULD NOT ASSURE CGMP'S WERE IN PLACE WHILE THERE WAS NOT EQUIPMENT INSTALLED. IT WAS STATED WE DID NOT AGREE WITH THAT POSITION NOR DID WE KNOW OF A REGULATION THAT REQUIRED ALL EQUIPMENT BE IN PLACE AND MIGHT CONTINUE A DISCUSSION OF THIS ACTION WITH THE DISTRICT OFFICE. MS. SAXENIAN REQUESTED MR. FALLONE TO PREPARE A LETTER TO THE DISTRICT OFFICE STATING OUR PLANS FOR COMPLETION OF THE PROJECT. THE DISTRICT WOULD THE RESCHEDULE THE PAI. WE ASKED IF THE REVIEW OF THE NDA WOULD STOP. IT WAS MS. SAXENIAN'S OPINION THAT REVIEW WOULD CONTINUE SINCE SEPTEMBER 1996 WAS THE DATE ASSOCIATED WITH THE USER FEE.
		13-FEB-96	TEL	V-96	DR. PLACE REQUESTED THAT NYCOMED PROVIDE HIM, WITH A DISKETTE CONTAINING THE NDA STABILITY TABLES WHICH WERE SUBMITTED TO THE DIVISION ON 16-JAN-96. DRA INDICATED THAT NYCOMED WOULD SEND HIM THIS INFORMATION AS SOON AS POSSIBLE.
		15-FEB-96	SUB	V-96	RESPONSE TO FDA REQUEST FOR INFORMATION, DATED 13-FEB-96. DRA PROVIDED DR. PLACE WITH THE DISKETTE CONTAINING REVISIONS TO THE NDA STABILITY TABLES.
		20-FEB-96	TEL	V-96	DRA CONTACTED FDA TO FOLLOW-UP, ON THE WORDPERFECT DISKETTE SENT TO FDA ON 29-JAN-96. FDA IS HAVING A PROBLEM MANIPULATING THE DATA ON THE DISKETTE. DRA ASKED IF IT WOULD BE HELPFUL FOR PREMIER WORLDWIDE TO VISIT AND INVESTIGATE THE PROBLEM. FDA INDICATED IT WOULD NOT BE HELPFUL AND WILL FAX TO DRA A COPY OF THE TABLE FORMAT THEY ARE TRYING TO CREATE WITH THE DATA.

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		21-FEB-96	TEL	V-96	FDA INQUIRED ABOUT THE POSSIBILTY, OF SUBMITTING THE PK STUDY REPORT (59010-2-008) BEFORE THE MID-END OF MARCH. DRA INDICATED THE CLINICAL DEPARTMENT IS WORKING DILIGENTLY ON THE REPORT AND DOES NOT THINK IT CAN BE SUBMITTED EARLIER THAN PROMISED.
		22-FEB-96	TEL	V-96	DRA CONTACTED FDA REGARDING THE DATA FORMAT, ON THE DISKETTE PROVIDED TO FDA ON 29-JAN-96. DRA CONSULTED THE CLINICAL DEPARTMENT AND FOUND THAT EVEN THOUGH THE TABLES CAN BE READ IN WORDPERFECT, THE DATA IS FORMATTED IN ASCII AND THE INTEGRITY OF THE TABLE AFTER MANIPULATION IS COMPROMISED. DRA INDICATED THE DATA DOES NOT EXIST IN ANY OTHER FORMAT THAT CAN BE MANIPULATED THE WAY FDA DESIRES. FDA CALLED LATER TO ASK QUESTIONS REGARDING THE LAB DATA FOUND ON THE DISKETTE PROVIDED.
		26-FEB-96	TEL	V-96	DRA AND CLINICAL CALLED FDA TO FOLLOW-UP, ON QUESTIONS ASKED 22-FEB-96. CLINICAL EXPLAINED THERE ARE MULTIPLE TABLES FOR EACH ANALYSIS BECAUSE EACH TABLE REPRESENTS A DIFFERENT REFERENCE RANGE AND NOT ALL ANALYSES WERE CONDUCTED BY THE CENTRAL LAB. FDA ASKED HOW THE DATA FROM THE DIFFERENT LABS WAS NORMALIZED. CLINICAL INDICATED THE LAB VALUES ARE STANDARDIZED AGAINST REFERENCE RANGES. FDA ASKED OF THE SIGNIFICANCE OF THE "FLAGS" IN THE AE LISTINGS. CLINICAL INDICATED THAT ALL ADVERSE EVENTS WHICH FALL OUTSIDE CERTAIN STUDY PARAMETERS ARE FLAGGED DUE TO THE EVENTS PROBABLY NOT BEING RELATED TO THE STUDY DRUG.
		01-MAR-96	TEL	V-96	DR. PIERRO CALLED TO REQUEST THAT SEPARATE, STATISTICAL ANALYSES TABLE OF THE CLINICAL LAB VALUES BE PREPARED FOR THE PHASE 2 AND PHASE 3 DATA IN THE ISS. ROCCO BALLERINI INDICATED THAT HE WOULD DO THIS.
		04-MAR-96	TEL	V-96	FDA CALLED TO FOLLOW-UP ON A REQUEST, FROM CLINICAL ON 01-MAR-96. DRA INDICATED THEY WOULD FORWARD 3 SETS OF ANALYSES TO FDA TODAY. FDA ASKED IF THE INFORMATION WAS IN A WORDPERFECT TABLE. DRA RESPONDED THE INFORMATION WAS EXPORTED FROM SAS DATABASE AND WERE PROBABLY IN ASCII FORMAT. FDA INDICATED THEY WERE INTERESTED IN

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		04-MAR-96	TEL	V-96	"SHIFT" DATA FOR THE LAB VALUES FROM THE PHASE 3 TRIALS. FDA WOULD ALSO LIKE INFORMATION SIMILAR TO THAT CONTAINED IN TABLE 6.2.3.H OF THE ISS. AFTER COMPARING THE DATA PROVIDED WITH TABLE 6.2.3.H OF THE ISS, DRA CONTACTED FDA TO INFORM THEM THE DATA WAS IN A SIMILAR FORMAT BUT NOT SUBGROUPED ACCORDING TO L-N, N-H AND L-H. FDA INDICATED THIS WAS AN IMPORTANT SUBGROUPING. DRA WILL LOOK INTO THIS ISSUE.
		05-MAR-96	TEL	V-96	FDA REQUESTED THE STATUS OF THE REPORT, FOR THE 59010-2-008 PK STUDY. DRA INDICATED THE DRAFT OF THE REPORT WOULD SOON BE AVAILABLE FOR INTERNAL REVIEW. FDA ASKED IF IT WOULD BE POSSIBLE TO PROVIDE DR. LEE WITH A COPY OF THIS DRAFT. DRA WILL FOLLOW-UP ON THIS REQUEST.
		05-MAR-96	TEL	V-96	DRA INFORMED FDA THE PHASE 3 "SHIFT" TABLES, WILL BE ADDRESSED UPON THE RETURN OF THE RESPONSIBLE CLINICAL PERSONNEL. FDA REVIEWED THEIR REQUEST FOR DATA PRESENTED IN WORDPERFECT FORMAT AND THEY ARE SEEKING A TABLE SIMILAR TO 6.2.3.H IN THE ISS FOR EACH PHASE 3 STUDY. DRA WILL CONTINUE WORKING ON THE REQUEST.
		08-MAR-96	TEL	V-96	DR. PLACE CALLED TO DISCUSS PAI, READINESS OF THE NYCOMED MANUFACTURING SITES. DR. PLACE REQUESTED A COMMITMENT FOR PAI READINESS OF THE MCPHERSON, KS SITE.
		08-MAR-96	TEL	V-96	FDA CALLED TO INQUIRE ABOUT THE STATUS, OF THE PHASE 3 LAB TABLES THAT WERE REQUESTED EARLIER IN THE WEEK. FDA ALSO ASKED FOR GUIDANCE ON THE LOCATION WITHIN THE CANDA OF "FINAL DIAGNOSES." DRA WILL FOLLOW-UP ON BOTH ISSUES.
		08-MAR-96	TEL	V-96	DRA CONTACTED FDA TO OBTAIN MORE DETAILS, ON THE UNDERSTANDING OF THE RENSSELAER PRE-APPROVAL INSPECTION AND DETERMINE IF THERE WOULD BE ANY ADVERSE EFFECTS ON THE NDA REVIEW IN PROGRESS. . DISTRICTS HAVE A DEADLINE TO FORWARD A RECOMMENDATION FOR APPROVAL (OR NONAPPROVAL) NO LATER THAN 60 DAYS BEFORE

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		08-MAR-96	TEL	V-96	THE USER FEE DUE DATE. . THE RENSSELAER INSPECTION OCCURRED AT MONTH 5 BECAUSE DR. PLACE WAS UNDER THE ASSUMPTION THE PRODUCT WAS STILL CLASSIFIED AS 1P (PRIORTY-6 MONTH REVIEW). HE LEARNED OF THE CLASSIFICATION TO 1S MUCH LATER. . IF WE HAVE FORKNOWLEDGE, NOTIFY DR. PLACE OF NEW DATES FOR INSPECTION AT RENSSELAER, HE WOULD LIKE TO PARTICIPATE IN THE INSPECTION. . DR. PLACE HAS BEEN FOLLOWING THE PRODUCT FOR YEARS AND IS LOOKING FORWARD TO WORKING WITH US PROACTIVELY TO RESOLVE ANY OF HIS QUESTIONS WHEN HE IS CLOSER TO COMPLETING HIS REVIEW.
		11-MAR-96	TEL	V-96	FDA CALLED TO INQUIRE THE STATUS OF, THE PHASE 3 LAB VALUE "SHIFT" TABLE. FDA ALSO HAD QUESTIONS REGARDING THE LOCATION OF "FINAL DIAGNOSES" IN THE CANDA. CLINICAL EXPLAINED THE TABLE WAS COMPLETE AND WOULD BE FAXED SHORTLY. CLINICAL ALSO ADDRESSED THE CANDA ISSUES AND WILL INCLUDE THE APPROPRIATE VARIABLE NAMES IN THE FAX. FDA ALSO REQUESTED CLINCAL REPRODUCE TABLE 9.5.2.2.A. FROM STUDY 1 WITH ALL OF THE PHASE 3 STUDIES COMBINED. FDA INQUIRED ABOUT THE FORMULATION HISTORY AND THE LOCATION OF THIS INFORMATION WITHIN THE NDA. DRA WILL LOCATE THIS INFORMATION FOR HIM. FDA INDICATED THE INTERNAL TIMEFRAME FOR COMPLETION OF THE MEDICAL REVIEW BY 01-APR-96 AND THE CLINICAL PACKAGE SHOULD BE ON DR. LOVE'S DESK BY MID-JUNE.
		12-MAR-96	FAC	V-96	IN REFERENCE TO THE CANDA FOR TESLASCAN, DRA FAXED THE TABLE AND VAIABLE INFORMATION.
		13-MAR-96	TEL	V-96	DR. PIERRO CALLED FOR MARK KLINGER, IN MARK'S ABSENCE, DR. PIERRO ASKED TO BE TRANSFERRED TO ROCCO BALLERINI. DR. PIERRO DISCUSSED A PROBLEM WHICH HE IDENTIFIED WITH THE "SHIFT" TABLE, FAXED TO HIM ON 11-MAR-96 ROCCO BALLERINI SAID HE WOULD REVISE THE TABLE AND FAX IT ASAP.
		13-MAR-96	FAC	V-96	DRA FAXED THE FOLLOWING INFORMATION:, . TABLE GENERATED BY CLINICAL (SIMILAR TO TABLE 9,5,2,2A)

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		13-MAR-96	FAC	V-96	WITH ALL PHASE 3 STUDIES COMBINED . THE DEVELOPMENT PHARMACEUTICS SECTION OF THE NDA (VOL. 1.4,PGS 2-5) . AN IND SUBMISSION (07 MAY 1993; SERIAL NO. 035) DESCRIBING BRIDGING STUDIES BETWEEN THE ORIGINAL AND THE OPTIMIZED FORMULATIONS . THE REVISED "SHIFT" TABLE THIS INFORMATION WAS ALSO SENT AS A SUBMISSION ON 18-MAR-96
		14-MAR-96	TEL	V-96	FDA CALLED TO FOLLOW-UP ON THE REQUEST, OF 13-MAR-96. FDA QUESTIONED IF IT WAS POSSIBLE WITHIN THE CANDA TO CREATE A "TABLE OF ENHANCEMENT PATTERNS" FOR THE NINE DIFFERENT DISEASES IN WHICH TESLASCAN WAS USED. FDA FELT SUCH A TABLE WOULD ALLOW THEM BETTER TO CHARACTERIZE THE IMAGING FOR EACH DISEASE STATE. DRA INDICATED THEY WOULD CONSULT CLINICAL.
		14-MAR-96	TEL	V-96	MULTIPLE DATES: 14,15-MAR-96, 14-MAR-96: DRA CONTACTED FDA TO INFORM THEM WE WOULD BE SUBMITTING THE FINAL REPORT FOR THE 59010-2-008 PK STUDY IN THE NEXT WEEK. FDA REQUESTED A DESK COPY BE SENT DIRECTLY TO THE CSO SO IT COULD BE GIVEN TO DIRECTLY TO DR. LEE AND NOT BE HELD UP IN THE DOCUMENT CONTROL ROOM. 15-MAR-96: DRA CONTACTED FDA TO INFORM THEM THE SIZE OF THE PK AMENDMENT HAS INCREASED DUE TO 14 SUPPORTING STUDY REPORTS. DRA INDICATED THE REPORT WOULD BE FINALIZED NEXT WEEK AND THEN WOULD BE SUBMITTED. DRA ALSO STATED THEY WOULD FAX THE INFORMATION REQUESTED ON 12-MAR-96.
		15-MAR-96	TEL	V-96	CLINICAL AND DRA CONTACTED FDA TO ADDRESS, FDA'S QUESTIONS OF 13,14-MAR-96. CLINICAL REVIEWED THE CANDA SETTINGS NECESSARY TO DUPLICATE THE PATIENT VALUE WHICH ARE LISTED IN THE STATISTICS REPORT OF THE NDA. FDA ASKED CLINICAL ABOUT THE POSSIBILITY OF CREATING A "TABLE OF ENHANCEMENT PATTERNS." CLINICAL INDICATED IT WOULD BE POSSIBLE TO CREATE SUCH A TABLE BUT WOULD HAVE TO

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		15-MAR-96	TEL	V-96	MANIPULATE THE CANDA THEN RESPOND.
		18-MAR-96	SUB	V-96	RESPONSE TO FDA REQUEST FOR INFORMATION, DATED 11-MAR-96 AND 13-MAR-96. DRA PROVIDED THE FOLLOWING INFORMATION: 1. LABORATORY PARAMETER "SHIFT" TABLES FOR CLINICAL INFORMATION CONTAINED WITHIN THE CANDA 2. LISTING OF VARIABLES PERTINENT TO LOCATION OF THE "FINAL DIAGNOSES" IN THE CANDA 3. A TABLE GENERATED BY CLINICAL (SIMILAR TO TABLE 9.2.2.A) WITH ALL PHASE 3 STUDIES COMBINED (1 PAGE TEXT, 2 PAGES TABLE) 4. INFORMATION REGARDING THE FORMULATION HISTORY OF MANGAFODIPIR, SPECIFICALLY THE DEVELOPMENT PHARMACEUTICS SECTION OF NDA (VOL 1.4, PAGES 2-5) AND AN IND SUBMISSION (07 MAY 1993; SERIAL NO. 035) DESCRIBING BRIDGING STUDIES BETWEEN THE ORIGINAL AND THE OPTIMIZED FORMULATIONS FOLLOW-UP REQUEST OF 13-MAR-96: 1. A REVISED VERSION OF THE LABORATORY "SHIFT" TABLES
		18-MAR-96	TEL	V-96	MULTIPLE CONTACTS: 18-MAR-96: DRA INFORMED FDA THAT IF ALL GOES WELL, THE 59010-2-008 PK AMENDMENT SHOULD BE SUBMITTED THIS WEEK 19-MAR-96: DRA INFORMED FDA THAT SOME PROBLEMS HAD ARISEN AND THAT A SUBMISSION OF THE PK AMENDMENT THIS WEEK IS UNLIKELY. FDA REITERATED HIS CONCERN REGARDING OUR COMMITTMENT TO SUBMIT THIS AMENDMENT BY THE END OF THE MONTH
		20-MAR-96	TEL	V-96	DR. PIERRO CALLED TO ADK IF CLINICAL HAD A, CHANCE TO WORK UP THE "PATTERN OF ENHANCEMENT" TABLE. DR. PIERRO INDICATED HE WAS STILL HAVING PROBLEMS RECONCILING PATIENT NUMBERS USING THE INSTRUCTIONS WHICH WERE PROVIDED IN OUR LAST CONVERSATION WITH CLINICAL. DR. PIERRO ASKED IF WE COULD PROVIDE THE NUMBERS(N), AS WELL AS THE PERCENTAGES FOR THE SENSITIVITY AND SPECIFICITY TABLE WHICH DRA SUBMITTED 18-MAR-96. DRA STATED THEY WOULD CHECK WITH CLINICAL AND GET BACK TO HIM AS SOON AS POSSIBLE.

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		22-MAR-96	TEL	V-96	DR. PIERRO REQUESTED CLARIFICATION ON THE, FOLLOWING ITEMS: . NYCOMED ASSERTS THAT MRI IS AN ALTERNATIVE TO CT. DR. PIERRO WANTS TO KNOW THE PERCENT AGREEMENT BETWEEN MR AND CT REGARDING THE "TRACKING" OF INDIVIDUAL LESIONS . DR. PIERRO ASKED WHETHER UNENHANCED COMBINED MRI OR ENCHANCED MRI IMAGE SETS ARE MISSING THE SAME LESIONS AS THE CT IMAGE SETS. ALTERNATIVELY, IF ONE DETECTS LESIONS WITH MRI HOW DO WE KNOW WHETHER THE LESIONS SEEN ON CT ARE THE CAME LESIONS . DR. PIERRO IS UNABLE TO FIND THE TABLE WHICH LISTS LIVER SEGMENTS FOR THE BLINDED READS (COMPARABLE TO APPENDIX 3.4.8.3) . DR. PIERRO WOULD ULTIMATELY LIKE TO DETERMINE THE LESIONS IN A GIVEN LIVER SEGMENT BY MODALITY. DRA STATED THEY WOULD ADDRESS THE ITEMS, AS RETURN THE CALL
		26-MAR-96	TEL	V-96	MR. WILLIAMS (CSO) REQUESTED 4 DESK COPIES, OF THE 18-MAR-96 SUBMISSION.
		26-MAR-96	SUB	V-96	RESPONSE TO FDA REQUEST FOR INFORMATION, DATED 26-MAR-96. DRA PROVIDED SANTFORD WILLIAMS WITH FOUR (4) DESK COPIES OF 18-MAR-96 SUBMISSION.
	2.1	29-MAR-96	SUB	V. 97-100	DRA SUBMITTED AMENDMENT 2.1 FOR NDA 20-652, WHICH INCLUDED FINAL STUDY REPORT FOR PROTOCOL 59010-02-008 AND SUPPORTING ANALYTICAL METHODS REPORTS, ADDENDUM TO THE INTEGRATED SUMMARY OF SAFETY, AND REVISED DRAFT LABELING.
		01-APR-96	FAC	V-101	DRA FAXED A COPY OF THE AMENDMENT COVER, LETTER TO SANTFORD WILLIAMS AS REQUESTED.
		02-APR-96	TEL	V-101	FDA CALLED TO INDICATE THAT IT MAY BE, HELPFUL TO DR. SOBHAN IF NYCOMED WERE TO SEND HIM THE SAS PROGRAMS, AND VARIABLE DESCRIPTORS FOR STUDY 59010-2-001. THIS WOULD ALSO HELP FDA ADDRESS THE "PATTERNS OF ENHANCEMENT" ISSUE WHICH HE IS TRYING TO RESOLVE. DRA INDICATED THEY WOULD CONSULT WITH CLINICAL ABOUT PROVIDING THE CODE.

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		03-APR-96	SUB	V-101	RESPONSE TO FDA REQUEST FOR INFORMATION, DATED 02-APR-96. DRA SUBMITTED THE FOLLOWING: . A PRINTOUT OF THE SAS VARIABLE DECRIPTORS FOR THE INTEGRATED SUMMARY OF EFFICACY . A PRINTOUT OF THE SAS VARIABLE DESCRIPTORS FOR STUDY PROTOCOL 59010-001 . A COPY OF THE INSTRUCTIONS FOR USE OF THE ENCLOSED SAS PROGRAMS . TWO (2) DISKETTES CONTAINING THE SAS PROGRAM FOR THE APPRENDICES, IN-TEXT TABLES AND GRAPHS FOUND IN THE INTEGRATED SUMMARY OF EFFICACY
		03-APR-96	TEL	V-101	DRA INFORMED DR. SOBHAN THAT WE FAXED HIM, A HARDCOPY OF THE VARIABLE DESCRIPTORS FOR THE ISE AND STUDY 59010-2-001 FRO NDA 20-652.
		04-APR-96	TEL	V-101	DR. PIERRO REQUESTED AN ELECTRONIC VERSION, OF THE ADDENDUM TO THE ISS AND THE REVISED DRAFT LABELING WHICH WAS SUMITTED NDA 20-652, AMENDMENT 2.1 ON 29-MAR-96. DR. PIERRO ALSO REQUESTED THE ELECTRONIC VERSION OF THE ANNUAL REPORT. THIS REQUEST WAS ALSO DATED 05-APR-96.
		04-APR-96	TEL	V-101	DR. SOBHAN INFORMED DRA THAT HE WAS, HAVING PROBLEMS WITH THE INFORMATION CONTAINED ON THE DISKETTES WHICH WAS SENT ON 03-APR-96. FDA STATED THE DATASETS WHICH THEY HAD CONTAINED VERSION 6.08 OF THE SAS CATALOG OF FORMATS. DRA EXPLAINED THAT HE NEEDED 6.10 VERSION. DRA WOULD MAKE A COPY AND SENT TO HIM.
		05-APR-96	SUB	V-101	RESPONSE TO FDA REQUEST FOR INFORMATION, DATE 04, 05-APR-96. DRA PROVIDED A DISKETTE CONTAINING THE SAS TRANSPORT FILE AND SAS PROGRAM WHICH WILL ALLOW FORMAT CONVERSIONS TO THE SAS CODE PREVIOUSLY PROVIDED TO DR. SOBHAN ON 03-APR-96.
		08-APR-96	TEL	V-101	DR. SOBHAN REQUESTED THE SAS PROGRAM FOR, PROTOCOLS 59010-2-001 AND 59010-2-003.
		09-APR-96	SUB	V-101	RESPONSE TO FDA REQUEST FOR INFORMATION,

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		09-APR-96	SUB	V-101	DATE 04-APR-96. DRA PROVIDED TWO (2) DISKETTES AS REQUESTED BY DR. PIERRO. DISKETTE 1 - STUDY REPORT 2514 PROTOCOL 59010-2-008 AND ADDENDUM A-01 DISKETTE 2 - ADDENDUM TO ISS REVISED DRAFT LABELING
		09-APR-96	TEL	V-101	DR. SOBHAN CALLED TO REQUEST DIRECTIONS FOR, USING THE DISKETTE WHICH DRA SENT TO HIM ON 05-APR-96. DRA DETERMINED THAT DR. SOBHAN WILL REQUIRE A MACRO WHICH PREFORMS A STATISTICAL TEST ON THE DATA. DRA WILL SENT HIM THIS INFORMATION.
		09-APR-96	SUB	V-101	RESPONSE TO FDA REQUEST FOR INFORMATION, DATED 08-APR-96. DRA PROVIDED TWO (2) DISKETTES CONTAINING: DISKETTE 1 - THE SAS PROGRAMS FOR PROTOCOL 59010-2-001 DISKETTE 2 - THE SAS PROGRAMS FOR PROTOCOL 59010-2-003
		11-APR-96	TEL	V-101	DRA INQUIRED AS TO THE STATUS OF THE, PRECLINICAL AND CMC REVIEWS FOR TESLASCAN. DRA STATED THAT NYCOMED HAD BEEN GETTING NUMEROUS QUESTIONS FROM THE MEDICAL AND BIOSTATISTIC REVIEWERS, AND WERE CURIOUS AS TO HOW THE OTHER REVIEWS WERE PROCEEDING.
		12-APR-96	SUB	V-101	RESPONSE TO FDA REQUEST FOR INFORMATION, DATED 09-APR-96. DRA PROVIDED TO DR. SOBHAN A DISKETTE CONTAINING A MACRO TO PERFORM THE WILCOXON SIGN RANK TEST ON THE 59010-2 SAS DATASETS.
		15-APR-96	TEL	V-101	DR. PIERRO INFORMED DRA THAT DR. SOBHAN, IS HAVING DIFFICULTY UNDERSTANDING THE VARIABLE DESCRIPTORS FOR THE SAS CODE. DRA STATED THEY WILL CONTACT CLINICAL TO SEE IF THIS SITUATION COULD BE RESOLVED. DR. PIERRO CALLED ON 16-APR-96 TO INFORM DRA THAT DR. SOBHAN'S UNDERSTANDING OF THE SAS VARIABLES HAD IMPROVED.
		18-APR-96	TEL	V-101	DR. DAVID LEE CONTACTED DRA TO INTRODUCE, HIMSELF AS THE REVIEWER FOR SECTION 6.0 OF THE NDA. DR. LEE INDICATED HE HAD SEVERAL QUESTIONS BEFORE HE COULD CONTINUE

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		18-APR-96	TEL	V-101	THE REVIEW. . FDA WAS CONFUSED BY INCONSISTANT TERMINOLOGY FOR THE ADMINISTERED DOSE AND ASKED THAT THE TERMINOLOGY BE STANDARDIZED. . FDA REQUESTED CLARIFICATION WITH DESIGNATION THE UNITS UG EQUIVALENTS/HR/G. . REQUESTED DRA PROVIDE THE STANDARDS, STANDARD CURVES,QC AND VALIDATION INFORMATION FOR EACH ASSAY METHOD USED IN ALL THREE STUDIES FOR EACH ASSAY RUN. . FDA ASKED FOR AN EXPLAINATION AS TO HOW THE MANGANESE CONCENTRATION AT 0 HR CAN BE 2 UG/ML, THEN AT ONE MINUTE POST DOSING THE CONCENTRATION CAN DROP TO 0.98 UG/ML. . FDA WAS CONCERNED THAT WE DID NOT MEASURE ENDOGENOUS MN LEVELS IN STUDY REPORT 727 AND IS UNCLEAR AS TO HOW IT SHOULD BE REVIEWED. . FDA WOULD LIKE DRA TO SUBTRACT THE PREDOSE MN VALUES IN STUDY REPORT 727 AND RECALCULATE THE AUC. FDA INDICATED THE DATA POINT FOR SEVERAL PATIENTS WERE MISSING AND THE CALCULATION FOR THE MEAN WAS PERFORMED INCORRECTLY. . FDA ASKED IF THE COMMERCIAL FORMULATION WAS USED IN THE 59010-2-008 PK STUDY. . FDA ASKED THE LOCATION WHERE THE ISSUE OF DRUG INTERACTIONS WAS ADDRESSED. . FDA ASKED THAT WE "REVIEW AS A SCIENTIFIC EXERCISE THE CONCENTRATIONS OF MANGANESE IN THE PATIENTS ACROSS THE TWO STUDIES ONCE WE STANDARDIZED THE UNITS OF DOSE AND ASK OURSELVES IF THEY MAKE SENSE." FDA ASKED DRA TO PROJECT TIME LINES FOR THE SUBMISSION OF .THIS INFORMATION. DRA INDICATED CONSULTATION WITH THE DRUG METABOLISM GROUP WOULD BE NEEDED. FDA INDICATED THE INFORMATION IS REQUIRED BY 29-APR-96 OR IT WOULD AFFECT THE REVIEW.
		23-APR-96	TEL	V-101	DRA CONTACTED MR. WILLIAMS TO DETERMINE, DR. LEE'S AVAILABILITY FOR A CONFERENCE CALL. MR. LEE STATED HE WOULD CONTACTED DR. LEE PROPOSING A PHONE CONFERENCE AND WOULD ARRAGE IT TO COINCIDE WITH DR. LEE'S RETURN.
		29-APR-96	TEL	V-101	FDA CALLED IN REFERENCE TO STUDY REPORT 2514,

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		29-APR-96	TEL	V-101	HE ASKED FOR THE LOCATION OF THE POST-INJECTION PROTHROMBIN TIMES IN APPENDIX 4.3.6.3. THE TABLE CONTAINED IN THIS APPRNDIX CONTAINS ONLY BASELINE VALUES. DRA CONTACTED CLINIAL AND RETURNED FDA'S CALL STATING FOR PROTOCOL 008, PROTHROMBIN TIME WAS RECORDED ONLY AT "SCREENING" (BASELINE) NO POST-INJECTION PROTHROMBIN TIMES ARE AVAILABLE.
		01-MAY-96	TEL	V-101	CONFERENCE CALL BETWEEN MARK KLINGER, JUDY JOHNSON, BILL BLAZAK AND DR. LEE. DISCUSSIONS WERE AROUND THE FOLLOWING: (SEE CONTACT REPORT FOR DETAIL) . DR. LEE INDICATED THAT STANDARDS, STANDARD CURVES AND Q.C. DATA FOR ALL ASSAY METHODS USED TO DETERMINE DRUG LEVELS IN BIOLOGICAL SAMPLES (HUMAN PK STUDIES) SHOULD BE SUBMITTED ON A ROUTINE BASIS. . DR. LEE ASKED IF NYCOMED HAD CONDUCTED OR HAD PLANS TO CONDUCT ANY STUDIES WITH THIS AGENT IN RENALLY IMPAIRED PATIENTS
		06-MAY-96	TEL	V-101	DRA CONTACTED CSO TO DETERMINE THE STATUS OF, THE CMC AND PRECLINICAL REVIEWS FOR NDA 20-652. CSO STATED THAT ALL OF THE REVIEWS WERE ALMOST COMPLETED BY THE PRIMARY REVIEWERS. DRA MENTIONED THAT A TELECONFERENE WITH DR. LEE WAS HELD ON 01-MAY-96 AT WHICH TIME MOST OF DR. LEE'S QUESTIONS WERE ADDRESSED. THE CSO REQUESTED THAT WE PROVIDE HIM A COPY OF THE CONFERENCE MINUTES, AS HE WAS UNABLE TO ATTEND. DRA WILL PROVIDE AFTER THE MINUTES ARE FINALIZED.
		07-MAY-96	TEL	V-101	DR. LEE CALLED TO REQUEST ADDITIONAL, INFORMATION REGLATING TO STUDY REPORT 1587. DRA WILL INQUIRE ABOUT THE REQUESTED INFORMATION AND RETURN THE CALL
		10-MAY-96	TEL	V-101	FDA CALLED AND SPOKE WITH DRUG SAFETY, ASSEMENT WITH THE FOLLOWING QUESTIONS: . WHAT THE DIFFERENCE WAS BETWEEN PLASMA AND PLASMA-WATER AS DISCUSSED IN STUDY REPORT 1587 . ASKED ABOUT THE STATUS OF THE INFORMATION REQUESTED IN THE MAY 1ST TELECONFERENCE . ASKED IF THE HPLC RADIOGRAMS OF THE URINE AND

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		10-MAY-96	TEL	V-101	PLASMA-WATER METABOLITE PROFILES IN STUDY REPORT 1587 WERE REPRESENTATIVE OF ALL SUBJECTS. DSA PROVIDE ANSWERS TO FDA
		16-MAY-96	TEL	V-101	FDA CONTACTED DRA TO INDICATE THE REVIEW, WAS ALMOST COMPLETE. FDA INDICATED THE ONLY "DEFICIENCY" BEING EXPRESSED IN THE REPORT WILL BE LACK OF "COAGULATION POINT PARAMETER" DATA. THE REPORT WILL BE FORWARDED TO DRS. LOVE AND BOTSTEIN SOON. DRA ASKED FDA THEIR IMPRESSION OF THE CANDA. FDA STATED THE CANDA WAS GOOD FOR EVALUATING THE SAFETY OF THE DRUG. THE CANDA IS SIMPLE FOR SIMPLE EFFICACY QUERIES BUT DIFFICULT FOR COMPLICATED QUERIES, THE SAS DATA SETS WERE DIFFICULT FOR SOME OF THE EFFICACY EVALUATIONS THEY WISHED TO CONDUCT. FDA FELT THE PROBLEMS WERE DUE TO THE "COMPLEXITY" OF THE DATA SETS NOT THE FORMATTING OF THE CANDA.
		16-MAY-96	TEL	V-101	FDA CONTACTED DRA TO REQUEST A DISKETTE, CONTAINING DRAFT LABELING. FDA ASKED IF THE LABELING COULD BE PROVIDED IN 3-COLUMN FORMAT. DRA QUESTIONED THE 3-COLUMN FORMAT. FDA RESPONDED NYCOMED WOULD NEVER SEE THE THE 3-COLUMN FORMAT ONCE IT IS REISSUED FROM THE DIVISION. THE THIRD COLUMN IS USED BY THE DIVISION FOR INPUTTING RATIONALE FOR THEIR RESPONSES TO OUR CLAIMS. DRA WILL CHECK ON WHETHER THE LABELING COULD BE FORMATTED TO 3-COLUMN. DRA LATER RESPONDED TO FDA THE DRAFT LABELING WILL BE PROVIDED TO FDA THE WEEK OF 20-MAY-96 IN 3-COLUMN FORMAT. DRA ADDED AT THAT TIME, THEY WILL ALSO SEND A COPY OF THE MEETING MINUTES TO THE 01-MAY-96 TELECONFERENCE BETWEEN NYCOMED AND DR. DAVID LEE.
		17-MAY-96	TEL	V-101	FDA CONTACTED DRA TO REQUEST INFORMATION, ON THE FOLLOWING ISSUES; ANSWERS WERE PROVIDED AFTER CONSULTATION WITH CLINICAL: . DID WE CONDUCT A COMPARISON OF ADVERSE EVENTS BETWEEN THE "OLD" FORMULATION AND "NEW" FORMULATION? A COMPARISON OF ADVERSE EVENTS WAS NOT CONDUCTED, AS THE COMPANY FEELS THE TWO FORMULATIONS ARE NOT COMPARABLE. . WHY DID WE CONDUCT AN ANALYSIS OF INDIVIDUALS WHO WERE

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		17-MAY-96	TEL	V-101	PREDISPOSED TO SEIZURES? A RETROSPECTIVE SUBGROUP ANALYSIS OF INDIVIDUALS WAS CONDUCTED AT THE REQUEST OF A REVIEWER IN THE PRE-NDA MEETING.
		22-MAY-96	SUB	V-101	RESPONSE TO FDA REQUEST FOR INFORMATION, DATED 06-MAY-96 AND 15-MAY-96. DRA PROVIDED THE FOLLOWING: . A COPY OF THE MINUTES OF THE TELEPHONE CONFERENCE HELD ON 01-MAY-96 BETWEEN NYCOMED PERSONNEL AND DR. LEE OF THE DIVISION OF PHARMACEUTICAL EVALUATION II . A DISKETTE CONTAINING THE DRAFT LABELING FOR TESLASCAN IN 3-COLUMN FORMAT
		28-MAY-96	TEL	V-101	FDA CONTACTED DRA TO SPEAK WITH CLINICAL, REGARDING THE INSPECTIONS OF THE CLINICAL SITES FOR DRS. FEDERLE AND HARMON. FDA STATED THE DISCUSSION WAS TO BE AN INFORMAL ONE AND FDA WANTED TO INFORM OUR CLINICIANS OF THE DISCREPANCIES WHICH WERE FOUND IN THE INSPECTION. FDA INIDCATED THE DISCREPANCIES FOUND WILL NOT AFFECT THE NDA BUT MAY AFFECT FUTURE FILINGS. DRA WILL ARRANGE A PHONE CONFERENCE BETWEEN CLINICAL AND FDA.
		29-MAY-96	TEL	V-101	TELECONFERENCE BETWEEN CLINICAL AND FDA, INFORMAL DISCUSSION REGARDING THE INVESTIGATIONS OF THE CLINICAL SITES FOR DRS. FEDERLE AND HARMON. FDA ASKED IF THE STUDIES CONDUCTED AT THESE SITES WERE MONITORED BY A CRO. CLINICAL INDICATED THAT PAREXEL WAS MONITORING THESE SITES. FDA STATED THE INSPECTORS UNCOVERED DISCREPANCIES AND GAVE SUGGESTIONS TO THE INVESTIGATORS TO RECTIFY THEM. THE SUGGESTIONS WERE NOT IMPLEMENTED BY THE INVESTIGATORS. FDA SUGGESTED WE REQUEST COPIES OF THE 483'S. THE DISCREPANCIES FOUND AT DR. FEDERLE'S SITE FOLLOW: . "TIMEFRAMES" WERE NOT FOLLOWED FOR MRI EXAMS . EXAMS WERE NOT CONDUCTED IN THE ORDER SPECIFIED BY THE PROTOCOL . FOLLOW UP EXAMS WERE NOT CONDUCTED ON SOME PATIENTS. FDA SUGGESTED THAT IF A CLINICAL PROTOCOL PROVE TO BE UNWORKABLE, THAT IT BE AMENDED AND SUGGESTED DOCUMENTATION BE COMPLETE AS POSSIBLE. WHEN PATIENTS DO NO REPORT FOR A

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		29-MAY-96	TEL	V-101	FOLLOW-UP EXAM, WE SHOULD TRY TO DOCUMENT THAT ALL EFFORTS WERE MADE FOR THEM TO RETURN. THE DISCREPANCIES FOUND AT DR. HARMON'S SITE FOLLOW: . FILMS WERE READ TWICE WHEN THEY WERE ONLY SUPPOSED TO BE READ ONCE. THIS CREATED SOME CONFUSION FOR THE INSPECTORS. CLINICAL STATED THERE WAS SOME MISUNDERSTANDING BETWEEN NYCOMED AND DR. HARMON REGARDING WHO WAS TO PERFORM THE READS FOR THE CT AND MR FILMS. FDA STATED NO PROBLEM WITH THE MISUNDERSTANDING AS LONG AS THE DETAILS WERE ADEQUATELY DOCUMENTED. FDA STATED THE INSPECTIONS UNCOVERED MORE DISCREPANCIES THAN USUAL ON CLINICAL SITE INPECTIONS. FDA REITERATED NYCOMED SHOULD REQUEST COPIES OF THE 483'S AND STATED THE ESTABLISHMENT INSPECTION REPORT WILL BE AVAILABLE IN APPROXIMATELY A MONTH. CLINICAL THANKED FDA FOR THE TIME AND INFORMATION.
		30-MAY-96	TEL	V-101	SANTFORD WILLIAMS REQUESTED AN UPDATE ON, THE INFORMATION WHICH DRA PROVIDED DR. DAVID LEE, PER THE 01-MAY-96 TELECONFERENCE. MR. WILLIAMS INDCIATED THAT THE REVIEWERS ARE TRYING TO FINALIZE THERI REVIEWS BUT DR. LEE REQUIRES THE ADDITION INFORMATION. DRA WILL FOLLOW-UP ON THE STATUS OF THIS DATA WITH THE APPROPRIATE PEOPLE AND GET BACK TO MR. WILLIAMS.
		04-JUN-96	SUB	V-102	RESPONSE TO FDA INFORMATION REQUEST DATED, 18-APR, 01 MAY, 07 MAY, AND 10 MAY. DRA PROVIDED DR. LEE WITH THE FOLLOWING INFORMATION: . ANALYTICAL ASSAY PERFORMANCE DATA FROM THE CLINICAL TRIALS 095-1011, 59010-2-005, AND 59010-2-008 . SERUM PHARMACOKINETIC DATA FROM CLINICAL TRIAL 095-1011 . AUC CALCULATIONS FROM CLINICAL TRIAL 59010-2-005 . METABOLITE PROFILES FROM CLINICAL TRIAL 59010-2-005
		04-JUN-96	TEL	V-102	DRA CALLED FDA CSO TO INFORM HIM THAT THE, INFORMATION PACKET, WHICH WAS REQUESTED BY DR. DAVID LEE O 01-MAY-96, WAS BEING SUBMITTED TODAY. DRA INQUIRED IF IT WOULD BE POSSIBLE TO ARRANGE A TELEPHONE CONFERENCE WITH

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		04-JUN-96	TEL	V-102	DR. LEE, UPON RECEIPT OF SUBMISSION, AS THERE WAS INFORMATION CONTAINED IN THE SUBMISSION WHICH MAY REQUIRE ADDITIONAL CLARIFICATION. THE CSO INDICATED THAT HE WOULD FOLLOW-UP WITH DR. LEE REGARDING THE TELEPHONE CONFERENCE AND GET BACK TO DRA.
		06-JUN-96	TEL	V-102	DRA CONTACTED FDA TO DETERMINE IF HE HAD, RECEIVED THE SUBMISSION FOR DR. DAVID LEE. CSO INDICATED THAT HE HAS NOT YET RECEIVED IT, BUT WOULD CHECK WITH THE DOCUMENT CONTROL ROOM. DRA REQUESTED THAT NYCOMED BE INFORMED WHEN THE SUBMISSION ARRIVES SO A TELECONFERENCE CALL COULD BE ARRANGED.
		10-JUN-96	TEL	V-102	THIS TELEPHONE CONTACT REPORT WAS FAXED TO, NYCOMED CQRA ON 12-JUN-96. SUMMARY OF CONTACT REPORT: CONTACT WAS MADE BETWEEN FDA, BUFFALO DISTRICT PAI MANAGER AND NYCOMED, RENSSELAER TO ARRANGE A MEETING WITH MR. PODSADOWSKI TO REVIEW PROGRESS AGAINST NYCOMED'S COMMITMENTS RELATIVE TO THE SUSPENSION OF PAI FOR MANGAFODIPIR.
		17-JUN-96	TEL	V-102	FDA CALLED TO ASK IF ANY NEW CLINICAL, INFORMATION WAS GOING TO BE INCLUDED IN THE UPCOMING IND ANNUAL REPORT. DRA STATED THAT THE ONLY CLINICAL INFORMATION COVERED IN THE ANNUAL REPORT RELATED TO THE 59010-2-008 PK STUDY. IN LIGHT OF THIS, THE MEDICAL REVIEWER WOULD SIGN-OFF ON HIS MEDICAL REVIEW OF NDA 20-652 AND SEND IT TO MANAGEMENT. FDA INDICATED THERE WERE A FEW QUESTIONS FROM OTHER REVIEWERS.
		20-JUN-96	TEL	V-102	FDA CONTACTED DRA TO FIND THE LOCATION, WITHIN THE NDA OF THE PROTOCOLS FOR CLINICAL STUDIES 001, 002, 003, AND 004. DRA TOLD FDA WHERE THE PROTOCOLS COULD BE FOUND AND STATED THAT NYCOMED USUALLY INCLUDES A COPY OF THE STUDY PROTOCOL AS AN APPENDIX OF THE FINAL STUDY REPORT.
		25-JUN-96	TEL	V-102	DRA CALLED TO INFORM FDA THE PRE-APPROVAL, INSPECTION MAY SOON BE OCCURRING AT THE RENSSALAER, NY AND MCPHEARSON, KS MANUFACTURING SITES. DRA INFORMED FDA NYCOMED'S VP OF MANUFACTURING AND THE QA ADMINISTRATOR FROM

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		25-JUN-96	TEL	V-102	THE RENSSALAER SITE WERE SCHEDULED TO MEET WITH INDIVIDUALS FROM THE BUFFALO FDA DISTRICT OFFICE THIS WEEK TO DETERMINE WHEN THE PRE-APPROVAL INSPECTION AT RENSSALAER WOULD RESUME. DRA MENTIONED A PLANT SHUT-DOWN FOR THE MCPHERSON SITE. FDA INQUIRED AS TO THAT DATE. DRA LATER INFORMED FDA THE PLANT SHUT-DOWN WOULD TAKE PLACE 22-JUL-96 TO 02-AUG-96. DRA ASKED IF THERE WERE QUESTIONS OR ADDITONAL INFORMATION REQUIRED TO COMPLETE THE REVIEW. FDA MENTIONED HE IS NOT IN A POSITION TO PROVIDE COMMENTS ON THE REVIEW. FDA QUESTIONED IF DRA HAD ACCESS TO THE INTERNET AND PROVIDED DRA WITH HIS INTERNET ADDRESS.
		09-JUL-96	TEL	V-102	DRA CONTACTED CSO DETERMINE THE STATUS OF, THE REVIEW OF THE NDA FOR TESLASCAN. THE CSO INDICATED THAT HE COULD NOT PROVIDE MUCH NEW INFORMATION. HE DID INDICATE THAT THE ACTION PACKAGE IS TOGETHER, DR. LOVE IS CURRENTLY REVIEWING THE NDA AND HE WOULD LIKE TO FORWARD THE ACTION PACKAGE TO DR. BOTSTEIN IN TWO WEEKS.
		12-JUL-96	TEL	V-102	FDA CONTACTED DRA TO QUESTION IF OUR NDA, CONTAINED AN INTEGRATED SUMMARY OF EFFECTIVENESS (ISE). DRA STATED THAT THE NDA CONTAINED AN INTEGREATED SUMMARY OF EFFICACY. DRA OFFERED A COPY OF THE ISE. FDA ACCEPTED AND REQUESTED TWO COPIES OF THE ADDENDUM TO THE ISS ALSO BE SENT. FDA INDICATED THEY DID NOT RECEIVE THE USER FEE FOR THE NDA. DRA STATED THE USER FEE WAS SENT, BUT WILL LOOK INTO THE ISSUE FURTHER. DRA ASKED WHAT KIND OF INFORMATION IS CONTAINED IN THE "ACTION PACKAGE" THE DIVISION IS PREPARING. FDA EXPLAINED THE GENERAL INFORMATION INCLUDED IN THE PACKAGE.
		12-JUL-96	TEL	V-102	DRA CONTACTED FDA TO FOLLOW-UP THE CONTACT, EARLIER TODAY. FDA INDICATED IT WOULD NOT BE NECESSARY TO SEND COPIES OF THE ISE AND ADDENDUM TO THE ISS. DRA INFORMED FDA THE USER FEE HAD BEEN SENT SEVERAL MONTHS AGO AND HAS DOCUMENTATION THE CHECK WAS CASHED BY THE AGENCY. FDA INDICATED THERE WAS A PROBLEM WITH THE DOCUMENT ROOM AND THERE WAS NOT AN ISSUE WITH PAYMENT OF THE USER

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		12-JUL-96	TEL	V-102	FEE. DRA THANKED FDA FOR CLARIFYING THE ISSUES.
		15-JUL-96	TEL	V-102	CSO CALLED TO FOLLOW-UP ON DRA'S PREVIOUS, CONVERSATION (12-JUL-96) WITH SUSAN KUMMERER. DRA INFORMED CSO THAT MS. KUMMERER INDICATED THAT DRA SHOULD NOT SEND ADDITIONAL COPIES OF THE ISE AND ADDENDUM TO THE ISS. SHE ALSO CLARIFIED THE ISSUE REGARDING THE DIVISION'S RECEIPT OF THE USER FEE.
		16-JUL-96	TEL	V-102	DR. DAVID PLACE (CHEMISTRY REVIEWER) CALLED, TO REQUEST THE STATUS OF THE PAI SCHEDULE BY DISTRICT OFFICES.
		17-JUL-96	FAC	V-102	FDA FAXED TO DRA DRAFT TABLES PERTAINING TO, PATIENT INFORMATION TO BE FILLED OUT.
		17-JUL-96	TEL	V-102	CSO CALLED TO INFORM DRA THAT HE WOULD BE, FAXING A REQUEST FOR INFORMATION TO NYCOMED. THE REQUEST IS FOR SUMMARY PATIENT DATA WHICH DR. LOVE WILL USE TO CONFIRM INFORMATION CONTAINED WITHIN OUR DRAFT LABELING. CSO REQUESTED DRA FAX THE COMPLETED TABLE TO HIM, IN ADDITION TO MAKING A FORMAL SUBMISSION TO NDA. LATER IN THE DAY, DRA CALLED THE CSO TO INDICATE THE RECEIPT OF THE FAX.
		18-JUL-96	TEL	V-102	DRA CALLED FDA TO REQUEST CLARIFICATION, ON THE PATIENT INFORMATION WHICH WAS REQUESTED IN THE DIVISION'S FAX OF 17-JUL-96. FDA CALLED LATER IN THE DAY WITH ANSWERS TO DRA'S QUESTIONS (SEE CONTACT REPORT). SUBMISSION WILL FOLLOW WITH RESPONSE.
		22-JUL-96	TEL	V-102	DR. ERIC JONES AND MR. SANTFORD WILLIAMS, CALLED TO REQUEST THE PHASE 1 AND PHASE 2 ROI INTENSITY DATA OR THE LOCATION OF THIS DATA WITHIN THE NDA. DRA CALLED LATER IN THE DAY TO PROVIDE THE LOCATION OF THE DATA TO DR. JONES.
		23-JUL-96	TEL	V-102	DR. PLACE CALLED TO REQUEST THE STATUS OF, THE PAI AT RENSSALAER MANUFACTURING SITE. DRA INFORMED FDA THAT THE DISTRIC AGREED TO RESUME THE PAI BUT IT WAS NOT

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		23-JUL-96	TEL	V-102	KNOW WHETHER THE INSPECTION WOULD RESUME "WHERE IT LEFT OFF", OR WHETHER IT WOULD START FRESH.
		24-JUL-96	TEL	V-102	MULTIPLE CONTACTS: 24-JUL-96 - MR. WILLIAMS CALLED TO REQUEST THE STATUS OF THE TABLES WHICH HE FAXED TO NYCOMED. 25-JUL-96 - DRA CONTACTED ME. WILLIAMS TO TELL HIM THAT DRA WOULD BE FAXING HIM AN ACTION PLAN FOR SUBMISSION OF THE INFORMATION WHICH DR. LOVE REQUESTED.
		26-JUL-96	SUB	V-102	DRA PROVIDED AN UPDATE ON THE STATUS OF, THE INFORMATION REQUESTED IN THE FAX OF 17-JUL-96. DRA ANTICIPATES COMPLETING IT BY 09-AUG-96. THE FOLLOWING IS THE PROPOSED INFORMATION DRA WILL BE PROVIDING: . ADVERSE EVENT TABLE . TABLE 1, PATIENT DATA BY PHASE/FORMULATION . LAB VALUE TABLE
		26-JUL-96	FAC	V-102	DRA FAXED A COPY OF THE SUBMISSION DATED, 26-JUL-96 TO SANTFORD WILLIAMS (CSO) REGARDING THE UPDATE STATUS OF 17-JUL-96 FAX. DRA ASKED MR. WILLIAMS TO HAVE DR. LOVE REVIEW IT AND GIVE FEEDBACK TO NYCOMED.
		29-JUL-96	TEL	V-102	DRA INFORMED FDA THAT NYCOMED FAXED THE, DIVISION OUR ACTION PLAN FOR SUBMISSION OF THE INFORMATION REQUESTED ON 17-JUL-96
		30-JUL-96	TEL	V-102	DRA CONTACTED FDA TO FINALIZE PLANS FOR A, TELECONFERENCE WITH DR. LOVE TO DISCUSS THE CLINICAL TABLES FAXED TO NYCOMED ON 17-JUL-96 BY FDA.
		01-AUG-96	TEL	V-102	CSO CALLED TO UPDATE DRA ON THE POTENTIAL, TIMES FOR A PHONE CONFERENCE WITH DR. LOVE. THE CSO CALLED LATER IN THE DAY AND PROVIDED A DEFINITE TIME OF TO TO EXPECT A CALL FROM DR. LOVE. (11:45 01-AUG-96)
		01-AUG-96	TEL	V-102	DR. PATRICIA LOVE CALLED TO DISCUSS THE, ACTION PLAN WHICH WAS FAXED TO HER ON 26-JUL-96, AND SHE

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		01-AUG-96	TEL	V-102	AGREED TO EXCLUDE THE SAL-095-1011 DATA SET FROM THE POOLED DATA. DR. LOVE IS EXPECTING THAT DRA SUBMIT THIS INFORMATION ON OR BEFORE 09-AUG-96.
		09-AUG-96	TEL	V-102	DRA CALLED DR. DAVID PLACE TO PROVIDE HIM, AND UPDATE ON THE STATUS OF THE PAI IN RENSSELAER. DR. PLACE INDICATED THAT HE HEARD FROM THE INPSECTOR AT THE KANSAS CITY DISTRICT STATING THAT THEY ARE "CONDUCTING THEIR BUSINESS VERY WELL". HE ALSO ASKED THAT DRA KEEP HIM INFORMED OF THE STATUS OF THE PAI.
		12-AUG-96	SUB	V-102	RESPONSE TO FDA REQUEST FOR INFORMATION, 17-JUL-96. DRA PROVIDED THE FOLLOWING: . TABLES PROVIDING A SUMMARY OF ADVERSE EVENTS . TABLE WHICH CATEGORIZES PATIENT LAB DATA . TABLE WHICH CATEGORIZES PATIENT DISPOSITION BY FORMULATION . TABLE WHICH CATEGORIZES PATIENT VITAL SIGN DATA BY FORMULATION AND ALL FORMULATIONS COMBINED.
		13-AUG-96	TEL	V-102	DRA CONTACTED FDA TO INFORM DR. PLACE THE PRE-APPROVAL INSPECTION AT RENSSELAER WAS REINITIATED. DR PLACE INFORMED DRA THE INSPECTION WAS JUST "FINISHING UP" AND HE WILL NOT BE PARTICIPATING. DR PLACE IS NOW ALERTED TO WATCH FOR THE INSPECTION REPORT AND FINALIZE THE CHEMISTRY REVIEW FOR TESLASCAN.
		21-AUG-96	TEL	V-102	DRA CONTACTED FDA TO DISCUSS REVIEW STATUS, OF NDA AS WELL AS ISSUES WHICH DESIGNATED AN "ACTION" AS APPROVAL, APPROVABLE OR NON-APPROVABLE. HIGHLIGHTS OF DISCUSSION FOLLOW: . ANTICIPATE AN ACTION LETTER (APPROVABLE, BEST CASE) ON 13-SEP-96. . DRAFT QUESTIONS MOST LIKELY WILL NOT BE ISSUED PRIOR TO THAT DATE; EXPERIENCE HAS SHOWN THAT MAJOR CHANGES HAVE BEEN MADE WHEN BEING FINALIZED. . DIVISION HAS NOT ISSUED APPROVAL LETTERS AS A FIRST ACTION, IN THE LAST YEAR. NO APPLICATION HAS BEEN "CLEAN" ENOUGH TO DO THAT.

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		21-AUG-96	TEL	V-102	. USER FEE "ACTION" LETTERS ARE BEING MISINTERPRETED BY INDUSTRY. THE GOAL IS AN ACTION WITHIN 6 OR 12 MONTHS (IP OR IS DESIGNATION) BUT DOES NOT NECESSARILY MEAN APPROVAL. IF APPLICATIONS ARE VERY GOOD, WITH EASY QUESTIONS TO ANSWER, AN APPROVAL AS A FIRST ACTION IS POSSIBLE. . CMC REVIEW - AT SUPERVISORY LEVEL (COMMENTS) MICROBIOLOGY - SIGNED OFF PRECLINICAL - SIGNED OFF (LABELING COMMENTS) CLINICAL - REVIEW WITH TEAM LEADER (DR. JONES) EA - SIGNED OFF WITH COMMENTS
		23-AUG-96	LFF	BUFFALO DIST	BUFFALO DISTRICT OFFICE OF THE FDA HAS, RECOMMENDED APPROVAL OF THE NDA 20-652, MANGAFODIPIR TRISODIUM APPLICATION FOLLOWING COMPLETION OF AN FDA GMP INSPECTION. THE RECOMMENDATION IS FOR MANUFACTURING OF THE BULK PHARMACEUTICAL MANAFODIPIR TRISODIUM. THE FINAL DSCISION TO APPROVE THE APPLICATION WILL BE MADE BY FDA'S CDER.
		27-AUG-96	TEL	V-102	DRA INFORMED DR. PLACE OF THE OUTCOME OF, THE PAI AT RENNSELAER. DR. PLACE THEN PROVIDED INPUT ON HIS REVIEW OF THE CMC SECTION OF THE TESLASCAN NDA. DR. PLACE HAS SUGGESTIONS ON THE FOLLOWING: . METHODS VALIDATION SECTION . DRUG SUBSTANCE . SECTION 3.1.1.3.6 . D.I. AND DISTILLED H2O SYSTEMS . DESCRIPTION OF OSMOMETER AND METHOD OF USE IN MANUFACTURE OF DRUG PRODUCT . STATE RANGE OF SPECIFICATIONS (UPPER AND LOWER LIMIT) FOR ASCORBIC ACID AND FODIPIR . POST APPROVAL STABILITY MONITORING
		27-AUG-96	FAC	V-102	FDA FAXED REQUEST FOR INFORMATION REGARDING, CHARTS TO BE COMPLETED FOR PATIENT, LABORATORY AND ADVERSE EVENTS DATA.
		28-AUG-96	TEL	V-102	FDA CONTACTED DRA FOR CLARIFICATION ON DRUG,

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		28-AUG-96	TEL	V-102	CODE NUMBERS AND THE SUBMISSION DATED 12-AUG-96. . FDA ASKED THE SIGNIFICANCE OF S-095 TO THE WIN NO. 59010. DRA ANSWERED S-095 IS THE ACTIVE INGREDIENT BUT IS REALLY UNRELATED TO THE DESIGNATION FOR FORMULATION. . FDA REFERED TO THE 12-AUG-96 SUBMISSION AND ASKED IF DATA FOR STUDY SAL-095-1011 WAS INCLUDED IN THE POOLED DATA. DRA ANSWERED THE INFORMATION WAS INCLUDED.
		29-AUG-96	TEL	V-102	DRA CONTACTED FDA TO FOLLOW-UP ON THE DATA, TABLES SUBMITTED 12-AUG-96. DRA QUESTIONED IF THE DATA TABLES SUBMITTED ADDRESSED FDA'S QUESTIONS. FDA RESPONDED IF THERE WERE ADDITIONAL QUESTIONS, NYCOMED WOULD HEAR TODAY OR TOMORROW. FDA INDICATED DR. LOVE IS READY TO FORWARD THE ACTION PACKAGE TO DR. BOTSTEIN VERY SOON.
		29-AUG-96	TEL	V-102	MULTIPLE CONTACTS FOR ADDITIONAL INFORMATION, 11:00 A.M.- FDA CALLED TO INDICATE A TABLE WILL BE FAXED WHICH FDA WOULD LIKE COMPLETED BY 30-AUG-96. DRA REPLIED A QUICK TURN-AROUND COULD NOT BE GUARANTEED. 11:15 A.M.- DRA CONTACTED FDA TO INFORM THEM THE TABLE FAXED IS A DUPLICATE AND THE INFORMATION WAS SUBMITTED ON 12-AUG-96. DRA QUESTIONED IF THE RESPONSE WAS NOT ADEQUATE. 2:15 P.M.- FDA REPLIED TO DRA THERE WAS A MISUNDERSTANDING WITH THE FAXED TABLE AND THE INFORMATION WAS NOT REQUIRED AGAIN. FDA DID HAVE A FEW QUESTIONS . PAGE 40 OF 12-AUG-96 SUBMISSION, WHY NYCOMED LISTED 613 TOTAL PATIENTS WHEN NDA STATED 642 PATIENTS RECEIVED TESLASCAN. . FDA ASKED FOR CLARIFICATION OF THE NUMBER OF PATIENTS WITHDRAWN FOR ADVERSE EVENTS LISTED ON THIS TABLE. . FDA ASKED IF DATA FROM THE "EUROPEAN" STUDY WAS INCLUDED IN THE DATA TABLES SUBMITTED 12-AUG-96. 2:30 P.M.- DRA CONTACTED FDA TO ANSWER QUESTIONS ASKED EARLIER TODAY.

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		29-AUG-96	TEL	V-102	. THE 613 PATIENT TOTAL THAT APPEARS ON PAGE 40 OF 12-AUG-96 SUBMISSION DOES NOT REPRESENT ALL PATIENTS EXPOSED TO TESLASCAN, ONLY PATIENTS EXPOSED TO FORMULATION 59010-2. . NO PATIENTS WERE WITHDRAWN DUE TO ADVERSE EVENTS. . THE BYK GULDEN ("EUROPEAN STUDY") STUDY DATA WAS NOT INCLUDED IN THE 12-AUG-96 DATA TABLES NOR INCLUDED IN THE OVERALL DATABASE FOR THE NDA.
		29-AUG-96	FAC	V-102	FDA FAXED TO DRA A DUPLICATE DATA TABLE, NOTE: THIS TABLE WAS PREVIOUSLY FAXED TO DRA 17-JUL-96 AND SUBMITTED TO FDA 12-AUG-96.
		09-SEP-96	TEL	V-102	FDA CONTACTED DRA TO REQUEST PICTURES, DEMONSTRATING VARIOUS IMAGING PATTERNS IN LIVER LESIONS. THE FOLLOWING IMAGING PATTERNS ARE TO BE DEMONSTRATED: . HOMOGENEOUS IMAGING . INHOMOGENEOUS . NONHOMOGENEOUS (?) . NODULAR . LINEAR FDA REQUESTED THE PICTURES BE SENT THE NEXT DAY. DRA REPLIED NYCOMED DID NOT HAVE PICTURES, BUT COULD PRINT OUT COPIES OF THE COMPUTER IMAGES BUT THE RESOLUTION OF THE PRINTOUT MAY NOT BE VERY GOOD. FDA THEN ASKED FOR A VIDEO OF THE IMAGES. DRA WAS NOT SURE THAT WAS POSSIBLE AND OFFERED TO SEND OUR IMAGE BASE EXPERT TO THE FDA OR THE EXPERT COULD COACH FDA THOUGH THE IMAGE BASE TO ACCESS THE IMAGES REQUESTED. FDA ASKED NYCOMED TO PROVIDE PRINTOUTS AND IF THEY WERE NOT ADEQUATE, WE COULD THEN TRY AN ALTERNATIVE METHOD. FDA REQUESTED THREE (3) SETS OF PRINTOUTS. ONE FOR THE ARCHIVE. ONE FOR DRS. LOVE AND JONES. ONE FOR DR. BOTSTEIN.
		12-SEP-96	FAC	V-102	FDA FAXED TO DRA A COPY OF THE APPROVABLE, LETTER AND DRAFT LABELING.
		12-SEP-96	LFF	V-102	DRA RECEIVED THE APPROVABLE LETTER FROM FDA,

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		12-SEP-96	LFF	V-102	FDA STATED THE REQUEST INFORMATION WHICH NEED TO BE SUBMITTED BEFORE THE APPLICATION MAY BE APPROVED.
		12-SEP-96	SUB	V-102	RESPONSE TO FDA REQUEST FOR INFORMATION, DATED 09-SEP-96. DRA PROVIDED FDA WITH ONE COPY OF THE SEVEN (7) EXAMPLES OF LESION IMAGES DEMONSTRATING THE DIFFERENT PATTENS OF ENHANCEMENT. THE ADDITIONAL TWO (2) COPIES WILL BE PROVIDED AT A LATER DATE. S
		13-SEP-96	TEL	V-102	DR. LOVE AND MR. WILLIAMS CALLED TO BRIEFLY, REVIEW THE ACTION LETTER AND INDICATE THEIR AVAILABILITY TO FIELD QUESTIONS, IF AND WHEN WE HAD ANY.
		16-SEP-96	LTF	V-102	DRA ACKNOWLEDGE RECEIPT OF THE APPROVABLE, LETTER ON 12-SEP-96, AND INFORMED FDA THAT COMMENTS ARE UNDER CONSIDERATION AND NYCOMED WILL RESPOND TO THEM AS SOON AS POSSIBLE.
		17-SEP-96	FAC	V-102	FDA FAXED TABLE PAGE 13 OF THE APPROVABLE, LETTER WHICH WAS TITLED, "SAMPLE TABLE, COMPARISON OF TESLASCAN IMAGE PATTERNS WITH LESIONS THAT WERE HISTOLOGICALLY CONFIRMED".
		17-SEP-96	TEL	V-102	DRA INFORMED FDA THAT THERE SEVERAL ISSUES, ON WHICH NYCOMED NEEDED CLARIFICATION. . SECTION B OF THE APPROVABLE LETTER IS MISSING . TABLE ON PAGE 12 OF LETTER IS NOT COMPLETE . ADVERSE REACTIONS, PAGE 11 OF DRAFT LABELING - PLEASE CONFIRM THAT THE DIVISION IS REQUESTING RATES WHICH EXCEED 0.5% RATHER THAN 1.0% . PREGNANCY CATEGORY, PAGE 8 OF DRAFT LABELING (CLARIFICATION) . PROPOSED TELECONFERENCE TO DISCUSS KARL-FISHER METHOD.
		17-SEP-96	FAC	V-102	DRA FAXED THE LIST OF ISSUES WHICH DRA, NEEDS CLARIFIED WITH DIVISION REGARDING APPROVABLE LETTER FOR NDA 20-652 TESLASCAN
		20-SEP-96	TEL	V-102	CSO CALLED TO PROVIDE AN UPDAT ON OUR,

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		20-SEP-96	TEL	V-102	17-SEP-96 FAX REQUESTING CLARIFICATION ON ISSUES IN THE APPROVABLE LETTER.
		23-SEP-96	TEL	V-102	CSO INFORMED DRA THAT HE WAS PROVIDING A, DISKETTE CONTAINING THE DIVISION'S PROPOSED LABELING, AS WE REQUESTED. CSO INDICATED THAT THERE WAS NO NEW INFORMATION ABOUT OUR REQUESTS FOR A TELEPHONE CONFERENCE WITH DR. LOVE OR OUR REQUEST FOR FERRIDEX LABELING.
		24-SEP-96	TEL	V-102	A TELEPHONE CONFERENCE AS HELD WITH MEMBERS, OF THE ANALYTICAL SCIENCES DEPT. AND THE DIVISION'S REVIEWING CHEMIST TO PROPOSE A CHANGE T THE KARL-FISCHER METHOD AND SOLICIT INPUT FROM THE REVIEWING CHEMIST. THE REVIEWING CHEMIST AGREED WITH PROPOSED CHANGES TO KARL-FISCHER METHOD.
		25-SEP-96	SUB	V-102	RESPONSE TO FDA REQUEST FOR INFORMATION, DATED 09-SEP-96, DRA IS PROVIDED THE ADDITIONAL TWO COPIES OF THE HARDCOPY IMAGES OF DIFFERENT PATTERNS OF LESION ENCHANCEMENT.
		27-SEP-96	TEL	V-103	MULTIPLE DATES;, 27-SEP-96 - CSO CALLED TO INFORM DRA THAT DR. LOVE AND THE TOXICOLOGY TEAM LEADER WILL BE AVAILABLE ON 03-OCT-96 TO DISCUSS THE PREGNANCY CATEGORY FOR TESLASCAN PACKAGE INSERT. 02-OCT-96 - DRA CONTACTED CSO TO PROVIDE HIM A TELEPHONE NUMBER WHERE WE CAN BE REACHED FOR THE 03-OCT-96 CONFERENCE WITH DR. LOVE.
		03-OCT-96	TEL	V-103	CONFERENCE CALL BETWEEN NYCOMED AND FDA:, PARTICIPANTS INCLUDED FROM NYCOMED AND FDA ARE: NYCOMED - PAT HALEY, GEORGE BROWN, WILLIAM BLAZAK AND MARK KLINGER. FDA'S - PATRICIA LOVE, LARAINE MYERS AND SANTFORD WILLIAMS. ISSUES DISCUSSED: . THE DIVISON'S RATIONALE FOR CHANGING THE PREGNANCY CATEGORY FROM CATEGORY C TO CATEGORY D WAS PROVIDED BY THE SUPERVISORY TOXICOLOGIST AND DIVISION DIRECTOR. . SUPERVISORY TOXICOLOGIST DOES NOT DISTINGUISH BETWEEN

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		03-OCT-96	TEL	V-103	FETOTOXICITY AND TERATOGENICITY . DIVISION DIRECTOR BELIEVES PRECEDENT HAS BEEN SET BY DIVISION OF ONCOLOGY TO BASE PREGNANCY CATEGORY ON ANIMAL DATA IN THE ABSENCE OF HUMAN DATA . DIVISION DIRECTOR ENCOURAGED NYCOMED TO SUBMIT OUR ARGUMENT FOR PREGNANCY CATEGORY C ALONG WITH SUPPORTING DATA
		10-OCT-96	FAC	V-103	DRA FAXED TO FDA QUESTIONS REGARDING, ADVERSE REACTIONS AND REGARDING FDA'S REQUEST.
		10-OCT-96	TEL	V-103	DRA CONTACTED FDA FOR CLARIFICATION ON PAGE, 14 OF 18 OF THE DIVISION'S PROPOSED LABELING. FDA ASKED DRA TO FAX A COPY OF THE QUESTIONS AND THE PAGE OF PROPOSED LABELING IN QUESTION. DRA LATER CONTACTED FDA TO CONFIRM RECEIPT OF THE FAX. FDA CONFIRMED RECEIPT AND STATED AN ANSWER MAY BE PROVIDED BY TOMORROW MORNING.
		11-OCT-96	TEL	V-103	IN REFERENCE TO THE FAX THAT WAS SENT TO FDA, FDA CALLED TO INFORM NYCOMED OF THE REPSONES TO THE QUESTIONS REGARDING TESLASCAN LABELING.
		23-OCT-96	TEL	V-103	MULTIPLE CONTACTS: WITH MR. WILLIAMS (CSO), 23-OCT-96: DRA INQUIRED ABOUT THE NUMBER OF COPIES THAT THE FDA REQUIRED FOR THE TESLASCAN APPROVABLE LETTER RESPONSES. HE SAID HE WOULD VERIFY THE CORRECT NUMBER AND RETURN THE CALL. 24-OCT-96: MR WILLIAMS CALLED TO REQUEST 10 COPIES OF THE RESPONSES (6 FOR THE REVIEWERS AND 4 DESK COPIES) AS WELL AS 11 COPIES OF THE FIRST VOLUME 24-OCT-96: DRA CALLED MR. WILLIAMS AND SUGGESTED THAT NYCOMED SUBMIT 4 COPIES OF THE SUBMISSION IMMEDIATELY, TO BE FOLLOWED UP BY THE 6 ADDITIONAL COPIES NEXT WEEK. DRA QUESTIONED HIS REQUEST FOR 11 COPIES OF VOLUME 1. HE STATED HE WAS INTERESTED IN OBTAINING THE "SUMMARY VOLUME". HE RESTATED HIS INTEREST AND DRA SAID THEY WOULD FAX HIM THE TABLE OF CONTENTS TO ACQUAINT HIM WITH THE SUBMISSION.

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		24-OCT-96	FAC	V-103	DRA FAXED THE TABLE OF CONTENTS FOR THE, TESLASCAN APPROVALBE LETTER REPSONSES TO MR. WILLIAMS AS DISCUSSED EARLY IN THE DAY.
		28-OCT-96	SUB	V. 104-113	RESPONSE TO FDA REQUEST FOR INFORMATION, DRA PROVIDED RESPONSE TO THE APPROVABLE LETTER DATED 12-SEP-96. THIS SUBMISSION PROVIDED THE FOLLOWING: VOL 1. SUMMARY OF RESPONSES VOL 2. CLAIM FOR MARKET EXCLUSIVITY CLINICAL ISSUES BIOPHARMACEUTICS/PHARMACOKINETICS PHASE IV COMMITMENTS VOL 3. LABELING INTRODUCTORY PROMOTIONAL MATERIALS VOL 4. SAFTEY - RESPONSES AND CASE REPORT FORMS VOL 5/6. SAFETY - FINAL SAFETY UPDATE VOL 7. CMC VOL 8/9/10. ENVIROMENTAL ASSESSMENT CASE REPORT FORMS WERE SUBMITTED FOR THE FOLLOWING PROTOCOL: MNV005 - PATIENT NO. 036 MNV008 - 006 MNV009 - 015 MNV009 - 018 MNV012 - 005 MNV014 - 015
		29-OCT-96	TEL	V-114	MR. WILLIAMS (CSO) CALLED TO INDICATE THAT, HE RECEIVED THE RESPONSES TO THE APPROVABLE LETTER AND ASKED FOR GUIDANCE ON ITS DISTRIBUTION TO FDA REVIEWERS. HE ALSO REQUESTED AN ADDITIONAL COPY OF VOLUME 3.
		05-NOV-96	TEL	V-114	DRA CONTACTED FDA TO PROVIDE AN UPDATE, REGARDING THE 04-OCT-96 REQUEST FOR THE INSTRUCTION SET PROVIDED TO THE CLINICAL REVIEWERS. . DRA STATED WITHIN THE APPENDICES OF EACH OF THE FOUR PHASE 3 NDA CLINICAL STUDY REPORTS THERE WERE SECTIONS TITLES "BLINDED READ PROTOCOL" AND "BLINDED READ GUIDELINES". DRA STATED THEY WOULD FAX THE LOCATION AND A REPRESENTATIVE SAMPLE OF THE SECTIONS TO FDA.

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		05-NOV-96	TEL	V-114	. FDA INFORMED DRA THERE IS A NEW CSO. DRA WILL FAX THE INFORMATION TO THE NEW CSO. . DRA ASKED WHO WOULD BE CONDUCTING THE MEDICAL REVIEW OF THE RESPONSES SENT TO THE DIVISION 28-OCT-96. FDA STATED THE REVIEWER MAY BE DR. JONES.
		06-NOV-96	TEL	V-114	DRA CONTACTED THE NEW CSO TO REVIEW, THE 04-OCT-96 REQUEST FOR INFORMATION. DRA REVIEWED THE HIGHLIGHTS OF THE REQUEST AND STATED THERE WAS SOME CONFUSION REGARDING THE REQUEST, BUT DRA WAS PREPARED TO FAX SOME INFORMATION FOR REVIEW. DRA WILL FAX THE LOCATION WITHIN NDA 20-652 OF THE "BLINDED READ PROTOCOL" AND THE "BLINDED READ GUIDELINES" FOR EACH OF THE PHASE 3 CLINICAL PROTOCOLS. DRA WILL ALSO FAX THE BLINDED READ PROTOCOL AND BLINDED READ GUIDELINES FROM PROTOCOL 001 TO DETERMINE IF THIS IS THE INFORMATION THE REVIEWER NEEDED.
		07-NOV-96	LFF	V-114	FDA ACKNOWLEDGE RECEIPT ON 29-OCT-96 OF, 28-OCT-96 AMENDMENT TO NYCOMED'S NDA FOR TESLASCAN. THIS AMENDMENT CONTAINS ADDITIONAL INFORMATION SUBMITTED IN RESPONSE TO FDA'S 12-SEP-96, APPROVAL LETTER AND FDA CONSIDERS THIS A MAJOR AMENDMENT AND IT CONSTITUTES A FULL RESPONSE TO FDA'S LETTER. THEREFORE, THE DUE DATE UNDER THE PRESCRIPTION DRUG USER FEE ACT OF 1992 IS APRIL 29, 1997
		04-DEC-96	TEL	V-114	DRA CALLED MS. JORDON (CSO) TO DETERMINE, THE STATUS OF THE RESPONSES TO THE APPROVABLE LETTER SUBMITTED 28-OCT-96. MS. JORDAN INDICATED THAT THE RESPONSES HAVE BEEN DISTRIBUTED TO THE DISCIPLINES AND THAT THE FIRST MEETING TO DETERMINE THE STATUS OF THE RESPONSE WILL TAKE PLACE ON 11-DEC-96.
		12-DEC-96	TEL	V-114	DRA CONTACTED FDA TO DETERMINE THE OUTCOME, OF THE 11-DEC-96 INTERNAL FDA MEETING WITH THE PRIMARY REVIEWERS. THREE DISCIPLINES WERE DISCUSSED: ENVIRONMENTAL ASSESSMENT, CMC, AND PHARM/TOX. THE FOLLOWING INFORMATION WAS GIVEN TO DRA: . ENVIRONMENTAL ASSESSMENT: A FONSI WILL BE ISSUED. . CMC: DR PLACE REQUESTED THE CMC RESPONSES ON DISKETTE FOR

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		12-DEC-96	TEL	V-114	REVIEW. . PHARM/TOX: PREGNANCY CATEGORY (C OR D) HAS NOT BEEN DECIDED. THE ISSUE WILL BE DISCUSSED FURTHER BEFORE 25-DEC-96. THE CSO STATED THE DIVISION WOULD LIKE TO COMPLETE THE PRIMARY REVIEW BY 01-FEB-97 AND INDICATED A REVIEW WITHIN THE 6 MONTH TIMEFRAME SHOULD NOT BE A PROBLEM.
		13-DEC-96	SUB	V-114	RESPONSE TO FDA REQUEST FOR INFORMATION, DATED 12-DEC-96. DRA PROVIDED A DISKETTE CONTAINING THE CMC RESPONSES TO THE APPROVABLE LETTER SUBMITTED ON 28-OCT-96, WHICH WAS REQUESTED ON BEHALF OF DR. PLACE.
		24-DEC-96	TEL	V-114	FDA STATED THAT THE REPRODUCTIVE TOXICOLOGY, COMMITTEE MEETING TO DISCUSS THE PREGNANCEY CATEGORY FOR THE TESLASCAN PACKAGE INSERT WAS POSTPONED UNTIL 09-JAN-97.
		09-JAN-97	TEL	V-114	DRA CALLED CSO TO DETERMINE THE OUTCOME OF, THE 09 JANUARY REPRODUCTIVE TOXICOLOGY COMMITTEE MEETING. THE FINAL DECISION REGARDING PREGNANCY CATEGORY HAS NOT BEEN MADE. THE FINAL DECISION REGARDING PREGNANCY CATEGORY HAS NOT BEEN MADE. IT REQUIRES CONCULTATION AT OFFICE LEVEL AND MAYBE EVEN CENTER LEVEL. THE DIVISION BELIEVES CATEGORY D IS APPROPRIATE. INTERPRETATION OF THE PREGNANCY CATEGORY REGULATIONS IS PROBLEMATIC. THE DIVISION IS ALSO CONCERNED ABOUT THE LEVELS OF FREE MANGANESE.
		31-JAN-97	TEL	V-114	THE FINAL DECISION REGARDING THE PREGNANCY, CATEGORY FOR TESLASCAN WAS MADE BY MEMBERS AT OFFICE AND CENTER LEVELS. ALL MEMBERS AGREED THAT PREGNANCY CATEGORY D IS APPROPRIATE.
		11-FEB-97	TEL	V-114	MS. JORDAN CALLED TO REQUEST ELECTRONIC, COPIES OF TWO TABLES WITHIN THE RESPONSE TO APPROVABLE LETTER. THE DIVISION WOULD LIKE TO INCLUDE THESE IN OUR DRAFT LABELING.
		12-FEB-97	SUB	V-114	RESPONSE TO FDA REQUEST FOR INFORMATION, DATED 11-FEB-97. DRA PROVIDED A WORDPERFECT DISKETTE

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NDA Number: 20-652
NDA Description: MRI-LIVER LESIONS -INJ

Date(s): (01-JAN-55 -> 01-JAN-99)
Supplement No.(s): (0 -> XXX)
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Supp No.	Amend No.	Date	Comm. Type	Location	Abstract
		12-FEB-97	SUB	V-114	CONTAINING THE FOLLOWING INFORMATION: . THE TABLE ENTITLED " TISSUE CLASSIFICATIONFOR STUIDES 001 AND 002" FOUND ON PAGE 6 OF THE RESPONSE TO APPROVABLE LETTER DATED 28-OCT-96. . THE TABLE ENTITLED "SUMMARY OF SPECIFIC ADVERSE EVENTS" FOUND ON PAGES 8-10 OF THE RESPONSE TO APPROVABLE LETTER.
		13-FEB-97	TEL	V-114	MS. JORDAN CALLED TO REQUEST DATES FOR A, TELECONFERENCE WITH THE DIVISION DIRECTOR, TO REVIEW THE DIVISION'S RATIONALE FOR RECOMMENDING A PREGNANCY CATEGORY D FOR TESLASCAN.
		13-FEB-97	TEL	V-114	MD. JORDAN CALLED TO REQUEST DATES FOR A, TELECONFERENCE WITH THE DIVISION DIRECTOR, TO REVIEW THE DIVISION'S RATIONALE FOR RECOMMENDING A PREGNANCY CATEGORY D FOR TESLASCAN.
		21-FEB-97	TEL	V-114	DRA CONTACTED MS.JORDAN TO PROVIDE TIME, SLOTS FOR THE UPCOMING TELECONFERENCE WITH DR. LOVE TO DISCUSS THE TESLASCAN PACKAGE INSERT PREGNANCY CATEGORY.
		26-FEB-97	TEL	V-114	MULTIPLE CONTACTS:, 26-FEB-97: MS. JORDAN CALLED TO INDICATE THAT THE TELECONFERENCE WITH DR. LOVE TO DISCUSS THE TESLASCAN PREGNANCY CATEGORY HAS BEEN SCHEDULD FOR 13-MAR-97 AT 9:00 A.M. 28-FEB-97: MS. JORDAN CALLED BACK TO CONFIRM THE 13 MARCH DATE FOR THE TELCONFERENCE WITH DR. LOVE.
		06-MAR-97	TEL	V-114	DRA CONTACTED FDA TO ADDRESS SEVERAL ISSUES, . DRA ASKED IF THE DRAFT LABELING WAS FINALIZED BY THE DIVISION. FDA RESPONDED THERE MAY BE ISSUES WHICH WILL BE DISCUSSED IN THE 13 MARCH CLINICAL LABELING MEETEING. AFTER THE MEETING, THE CSO WILL PROVIDE DRA WITH A COMPREHENSIVE LIST OF QUESTIONS . DRA ASKED IF THE VERBIAGE FOR THE PREGNANCY CATEGORY, CONTRAINDICATIONS AND WARNING SECTIONS HAVE BEEN CHANGED SUBSEQUENT TO THE APPROVABLE LETTER AND ASKED FOR A COPY OF THE NEW VERBIAGE PRIOR TO THE 13 MARCH TELECONFERENCE.

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		06-MAR-97	TEL	V-114	CSO WILL CHECK IF CHANGES WERE MADE AND REPLY TO DRA. . THE 13 MARCH TELECONFERENCE WAS POSTPONED BY DR. LOVE DUE TO OTHER PRIORITIES. DRA WLL CHECK ON NEW DATES FOR THE TELECONFERENCE.
		12-MAR-97	TEL	V-114	DRA CONTACTED FDA TO ADVISE THAT MALLINKRODT, HAS DISCONTINUED THEIR PROMOTIONAL ACTIVITIES FOR HEXABRIX. FDA STATED THEY WERE AWARE NYCOMED WOULD BE WORKING WITH BERLEX ON THE LAUNCH OF MANGAFODIPIR. FDA ADVISED BERLEX IT WOULD BE BENEFICIAL IF BOTH COMPANIES WORKED TOGETHER VS. DDMAC RATHER THAN TWO. FDA POINTED OUT IT WOULD SAVE TIME AND TROUBLE. FDA ALSO EXPAINED THE PROCESS FOR HANDLING THE LAUNCH AS SEPARATE COMPANIES.
		14-MAR-97	TEL	V-114	MULTIPLE DATES;, 14-MAR-97 - . LABELING MEETINGS AT THE DIVISION ARE COMPLETE CSO IS FORMALIZING QUESTIONS AND PHASE 4 COMMITMENTS. NYCOMED SHOULD RECEVIE THE DIVISION'S QUESTIONS BY 18-MAR-97. . COPY OF ENTIRE DRAFT LABELING WILL BE PROVIDED LAST WEEK OF MARCH. . RESCHEDULED TELECONFERENCE WITH DR. LOVE IS BEING OPENED UP TO DISCUSS ENTIRE DRAFT LABELING EVEN THOUGH DR. LOVE WOULD LIKE TO CONCENTRATE ON THE PREGNANCY CATEGORY. 1.5 HOURS IS BEING SCHEDULED FOR THIS MEETING. 17-MAR-97 - . CSO IS INVESTIGATING THE POSSIBILITY OF HAVING THE TELECONFERENCE ON THE MORNING OF 04-APR-97
		19-MAR-97	TEL	V-114	FINAL DATE OF DRAFT LABELING TELECONFERENCE, THE TELECONFERENCE WITH DR. LOVE HAS BEEN CONFIRMED FOR 24-APR-97, FROM 1:30 TO 2:30 P.M. THE CSO IS TRYING TO PROVIDE NYCOMED WITH THE DIVISIONS' QUESTIONS BY 21-MAR-97
		21-MAR-97	FAC	V-114	FDA FAXED THE DIVISION'S REQUEST FOR, . PHASE 4 COMMITMENTS AND TO RESPOND IN WRITING. . RESPONSE TO THE COMMENT MADE BY THE BIOPHARMACOLOGY/ PHARMACOKINETICS REVIEWER AND PROVIDE THE REQUESTED

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		21-MAR-97	FAC	V-114	INFORMATION.
		25-MAR-97	TEL	V-114	FDA CONTACTED DRA TO REQUEST MOST RECENT, VERSION OF THE VIAL AND CARTON LABELS. DR. LOVE WILL NOT BE ABLE TO PROVBIDE A COPY OF THE DRAFT LABELING THIS WEEK BUT ANTICIPATED PROVIDING IT PRIOR TO THE TELECONFERENCE ON 24-APR-97.
		27-MAR-97	TEL	V-114	DRA INFORMED FDA THE VIAL AND CARTON LABELS, HAVE NOT CHANGED FROM THOSE SUBMITTED IN THE NDA. DRA SOUGHT CLAIFICATION FROM THE CSO REGARDING NYCOMED'S RESPONSE TO THE DIVISIONS QUESTIONS WHICH WERE FAXED ON 21-MAR-97. THE CSO EMPHASUZED THAT DR. JONES WAS NOT SATISFIED WITH OUR ORIGINAL RESPONSED TO THE COMMITMENTS. DR. JONES HAS REQUESTED OUR RESPONSE TO THE PHASE 4 COMMITMENTS AS SOON AS POSSIBLE. THE DIVISION WOULD LIKE TO RESOLVE PHASE 4 ISSUES PRIOR TO ANY ISSUES WHICH MAY ARISE REGARDING THE DRAFT LABELING. A COPY IOF THE CURRENT VIAL AND CARTON LABELS WILL BE PROVIDED TO THE DIVISION.
		28-MAR-97	FAC	V-114	DRA FAXED TO FDA COPIES OF THE VIAL, AND CARTON LABELS.
		15-APR-97	SUB	V-114	RIR: PHASE 4 COMMITMENTS, DRA PROVIDED RESPONSES TO THE FAX OF 20-MAR-97 REQUESTING INFORMATION REGARDING PHASE 4 COMMITMENTS.
		16-APR-97	TEL	V-114	DRA CONTACTED FDA TO INFORM, . ON 15-APR-97 NYCOMED SUBMITTED RESPONSES TO THE PHASE 4 COMMITMENTS. . THE CSO INIDCATED NYCOMED SHOULD BE RECEIVING A COPY OF THE DRAFT LABELING BY THE END OF THIS WEEK. . DRA ASKED FDA TO ALERT THE REVIEWING CHEMIST TO A POTENTIAL TELECONFERENCE BETWEEN HIM AND NYCOMED PERSONNEL.
		22-APR-97	TEL	V-114	FDA CONTACTED DRA REGARDING THE STATUS OF, THE ACTION PACKAGE. FDA INDICATED THAT THE DRAFT LABELING

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		22-APR-97	TEL	V-114	WAS FAXED TO NYCOMED. DR. LOVE MENTIONED THAT THE PREGNANCY CATEGOTY HAS BEEN CHANGES FROM CATEGORY D TO CATEGORY C. DR. LOVE IS EXPECTING A WRITTEN RESPONSE FROM NYCOMED REGARDING A COMMITMENT TO CONDUCT A PHASE 4 STUDY IN PEDIATRIC PATIENTS.
		22-APR-97	FAC	V-114	FAX FROM FDA: DRAFT LABELING FOR TESLASCAN.
		23-APR-97	FAC	V-114	DRA FAXED TO FDA A BRIEF NARRATIVE, DESCRIBING TESLASCAN "FILM" ISSUE.
		23-APR-97	TEL	V-114	DRA CONTACTED THE CSO TO UPDATE HER ON, SEVERAL ISSUES. DRA MENTIONED THE DRAFT LABELING WAS DISTRIBUTED TO THE TEAM AND MENTIONED THE PHASE 4 COMMITMENT TO THE CLINICAL STAFF. DRA MENTIONED THE CMC ISSUE WAS DISCUSSED IN A MEETING AND REQUESTED CONTACT WITH DR. PLACE. . DR. PLACE WAS APPRISED OF THE TESLASCAN "RING" PHENOMENOM DRA AGREED TO ARRANGE A TELECONFERENCE BETWEEN NYCOMED CHEMISTS AND FDA CHEMISTS FOR 3:30 PM TODAY. DR. PLACE WAS FAXED A BRIEF NARRATIVE DESCRIBING THE RING PHENOMENON.
		24-APR-97	FAC	V-114	DRA FAXED TO FDA A COPY OF THE DRAFT, LABELING IN DOUBLE COLUMN FORMAT. ANNOTATIONS WERE MADE IN THE RIGHT HAND COLUMN INDICATING SECTIONS WHICH NYCOMED NEEDS CLARIFICATION OR REQUIRES SOME DISCUSSION.
		24-APR-97	TEL	V-114	TELECONFERENCE BETWEEN FDA AND NYCOMED, DISCUSSING THE FOLLOWING: INFORMATION FOR PATIENTS SECTION, ITEM 4; LAB TEST INTERACTIONS; ADVERSE REACTIONS SECTION; DOSAGE AND ADMINISTRATION SECTION; PEDIATRIC PHASE 4 STUDY; ELIMINATION SECTION;DISTRIBUTION SECTION; NURSING MOTHERS SECTION; ESSENTIAL AGREEMENT TABLES-SENSITIVITY AND SPECIFICITY TABLE.
		25-APR-97	SUB	V-114	DRA SUBMITTED REVISED DRAFT LABELING, FOR TESLASCAN DATED 25-APR-97. CHANGES FROM THE 22-APR-97 FDA DRAFT LABELING ARE HIGHLIGHTED AND COMMENTS APPEAR IN

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		25-APR-97	SUB	V-114	THE RIGHT COLUMN. THREE ATTACHMENTS ARE INCLUDED WITH THIS SUBMISSION: ATTACHMENT 1 - NEUROTOXICITY STATEMENT AND THE NURSING MOTHERS STATEMENT ATTACHMENT 2 - TABLE WHICH LISTS THE COMPONENTS OF SEVERAL COMMERCIAL INFANT FORMULATIONS ATTACHMENT 3 - TABLE "CORRECT CHARACTERIZATION OF LESIONS WITH KNOWN PATHOLOGY"
		25-APR-97	SUB	V-114	RIR: PHASE 4 COMMITMENT, DRA SUBMITTED THE COMMITMENT TO EXPLORE UNDERSTANDING THE USE OF TESLASCAN IN THE PEDIATRIC POPULATION (NEONATES AND CHILDREN.
		25-APR-97	TEL	V-114	DR. PLACE DISCUSSED WITH DR. SANTILLO, OF NYCOMED, THE DATA WHICH WAS SENT TO DR. PLACE ADDRESSING THE DISCOLORED "RING."
		29-APR-97	FAC	V-114	FDA FAXED TO DRA A COPY OF THE APPROVABLE, (ACTION) LETTER AND LABELING.
		29-APR-97	LFF	V-115	APPROVABLE LETTER FROM FDA, FOR NEW DRUG APPLICATION DATED 08-SEP-95. LETTER OUTLINED THE DEFICIENCIES AND TO SUBMIT FINAL PRINTED LABELING.
		02-MAY-97	SUB	V-115	GC: NYCOMED ACKNOWLEDGED RECEIPT OF THE, APPROVALBE LETTER AND FDA COMMENTS ARE UNDER CONSIDERATION. NYCOMED WILL RESPOND AS SOON AS POSSIBLE.
		05-MAY-97	TEL	V-115	THE CSO WAS CONTACTED FOR DATES FOR TWO, COMMUNICATIONS WITH THE DIVISION. ONE FOR A TELECONFERENCE WITH DR. LOVE TO DISCUSS LABELING ISSUES. THE OTHER TO SCHEDULE A MEETING WITH THE DIVISION'S CHEMISTS TO DISCUSS SOLUTIONS TO THE CMC ISSUE.
		05-MAY-97	TEL	V-115	FDA CONTACT DRA WITH DATES SCHEDULED FOR, THE TELECONFERENCE AND MEETING. . TELECONFERENCE WITH DR. LOVE IS SCHEDULED FOR 4:00 PM ON 07-MAY-97.

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		05-MAY-97	TEL	V-115	. MEETING WITH THE DIVISION'S CHMEISTS IS SCHEDULED FOR 2:00 PM ON 15-MAY-97. ANY INFORMATION FOR REVIEW SHOULD BE SENT TO THE DIVISION BY 11:00 AM ON 08-MAY-97 OR THE MEETING WILL BE CANCELED.
		06-MAY-97	TEL	V-115	FDA CALLED TO CHECK ON STATUS OF THE CMC, ACTION PLAN. DRA INDICATED THE CMC ACTION PLAN WOULD BE PROVIDED ON 07-MAY-97.
		08-MAY-97	SUB	V-115	GC: INFORMATION PACAKGE FOR REVIEW, IN PREPARATION FOR THE 15-MAY-97 MEETING BETWEEN NYCOMED AND THE DIVISION TO DISCUSS CHEMISTRY, MANUFACTURING AND CONTROLS ISSUES.
		08-MAY-97	TEL	V-115	DRA CONTACTED THE CSO TO REVIEW NYCOMED'S, INTENT OF THE CMC ACTION PACKAGE. THE CSO ALSO REQUESTED ADDITIONAL TIME FROM THE SUPERVISORY CHEMIST FOR SUBMISSION OF NEW DATA. IT WAS AGREED THE NEW DATA COULD BE SUBMITTED NO LATER THAN 12:00 PM 09-MAY-97.
		09-MAY-97	TEL	V-115	FDA WAS CALLED TO INFORM THEM THE CMC, ACTION PACAKGE WAS FAXED TO THE DIVISION. LATER DR. PLACE CALLED TO CONFIRM RECEIPT OF THE ACTION PACKAGE AN RAISED THREE ADDITIONAL ISSUES: . IS THERE ANY SCIENTIFIC PRECEDENCE OF THIS PHENOMENON IN THE LITERATURE? . IS THERE A DIFFERENCE IN THE OXYGEN CONCENTRATION OF THE HEADSPACE OF INVERTED VIALS VS. VIALS STORED RIGHT-SIDE UP? . CAN THE VIALS BE AUTOCLAVED UPSIDE-DOWN? DRA WILL COMUNICATE THE QUESTIONS TO THE NYCOMED CHEMISTS AND GET BACK TO HIM.
		13-MAY-97	TEL	V-115	DRA INDICATED THERE WERE A COUPLE OF ISSUES, TO BE DISCUSSED. . DRA ASKED IF THE MEETING FOR 15-MAY-97 IS STILL SCHEDULED THE DIVISION'S CHEMISTS DO NOT BELIVE ANY NEW DATA WAS PROVIDED AND QUESTION THE BENEFITS OF HAVING A FACE-TO-FACE MEETING. IT WOULD BE NYCOMED'S DECISION TO HAVE A

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		13-MAY-97	TEL	V-115	MEETING OR TELECONFERENCE. . DRA MENTIONED NYCOMED HAD SOME ORGANIZATIONAL CHANGES AND WOULD FAX A NEW LIST OF ATTENDEES.
		14-MAY-97	FAC	V-115	FAC: DRA FAXED THE REVISED LIST, OF PARTICIPANTS FOR THE 15-MAY-97 CMC MEETING.
		30-MAY-97	SUB	V-115	RIR: NYCOMED SUBMITTS RESPONSE TO APPROVALBE, LETTER RECEIVED 29-APR-97. SUBMISSION CONTAINS: . CMC RESPONSES WITH SUPPORTIVE DOCUMENTATION AND NDA CMC SECTIONAL LISTING . LABELING RESPONSES WITH ANNOTATED REVISED DRAFT LABELING AND REVISED DRAFT LABELING . PHASE 4 COMMITMENT RESPONSES.
		04-JUN-97	TEL	V-115	FDA CONFIRMED RECEIPT OF NYCOMED'S RESPONSE, TO THE 29-APR-97 APPROVABLE LETTER.
		09-JUN-97	LFF	V-115	LETTER FROM FDA ACKNOWLEDGING RECEIPT, ON 02-JUN-97 OF THE 30-MAY-97 RESPONSE TO THE APPROVABLE LETTER. FDA CONSIDERS THIS SUBMISSION A MAJOR AMENDMENT AND CONSTITUES IT A FULL RESPONSE TO THE ACTION LETTER. THE DUE DATE UNDER THE PRESCRIPTION DRUG USER FEE ACT OF 1992 IS 02-DEC-97.
		16-JUN-97	TEL	V-115	DRA CONTACTED FDA FOR AN UPDATE ON THE, STATUS OF THE 30-MAY-97 RESPONSE TO APPROVABLE LETTER. THE CSO WAS UNAWARE OF ANY NEW INFORMATION.
		23-JUN-97	TEL	V-115	DRA CONTACTED FDA TO INQUIRE THE STATUS, OF THE 30-MAY-97 RESPONSE TO APPROVABLE LETTER. THE CSO INDICATED THAT THE REVIEWING CHEMIST HAD COMPLETED HIS REVIEW AND WOULD LIKE TO CONFER WITH DRS LOVE AND LEUTZINGER BEFORE HE PROVIDES FEED-BACK TO NYCOMED.
		25-JUN-97	TEL	V-115	THE CSO HAS INDICATED THAT THE REVIEWING, CHEMIST WILL PROVIDE HIS REVIEW TO THE SUPERVISORY CHEMIST BY 28-JUN-97. THE SUPERVISORY CHEMIST HOPES TO PROVIDE NYCOMED WITH RESPONSES BEFORE 04-JUL-97. NYCOMED WILL NEED

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		25-JUN-97	TEL	V-115	TO RESOLVE ISSUES BEFORE THE DECEMBER ACTION DATE.
		01-JUL-97	TEL	V-115	DRA ASKED THE CSO FOR AN UPDATE OF REVIEW, FOR TESLASCAN. THE CSO INIDCATED DR. LOVE WOULD BE MEETING WITH DR. LEUTZINGER AT 3:00PM TODAY TO ADDRESS THE ISSUES. THE CSO WILL CONTACT DRA TOMORROW, 02-JUL-97 AND REPORT THE OUTCOME OF THE MEETING.
		08-JUL-97	TEL	V-115	TENTATIVE DISCUSSIONS WITH THE CSO, REGARDING TESLASCAN CMC ISSUES INDICATE THAT THE DIVISION WILL REQUIRE ADDITIONAL STUDIES TO INVESTIGATE ALTERNATE CLOSURE SYSTEMS, AND MAY REQUIRE ADDITIONAL STUDIES TO MONITOR THE HEADSPACE OXYGEN LEVELS OVER TIME.
		23-JUL-97	TEL	V-115	THE CSO PROVIDED AND UPDATE ON THE REVIEW, THE REVIEWING CHEMIST COMPLETED HIS REVIEW. THE CHEMISTRY MEETING WITH DR. LOVE WAS RESCHEDULED FOR THE AFTERNOON OF 30-JUL-97. ADDTIONAL STUDIES REGARDING CONTAINER/CLOSURE SYSTEMS AND HEADSPACE OXYGEN WILL BE REQUIRED, HOWEVER, NO DETAILS COULD BE PROVIDED AT THIS TIME.
		01-AUG-97	TEL	V-115	THE CSO WAS CALLED TO DETERMINE THE, OUTCOME OF THE CMC MEETING HELD 30-JUL-97 AT THE DIVISION. THE MEETING WAS HELD WITH NO CONSENSUS BEING REACHED. DIVISION REQUESTED INPUT FROM THE OFFICE LEVEL CHEMIST. UPON DECISION BY OFFICE LEVEL CHEMIST, DIVISION MUST MAKE PROPOSAL TO DR. BOTSTEIN FOR FINAL APPROVAL. NO TIME TABLE HAS BEEN SET FOR RESOLUTION OF THIS ISSUE, BUT DIVISION DIRECTOR IS PUSHING FOR A RESOLUTION AS SOON AS POSSIBLE.
		06-AUG-97	TEL	V-115	THE CSO CALLED TO PROVIDE A CMC UPDATE, . MEETING WITH OFFICE LEVEL CHEMIST WAS HELD. DR.GIBBS HAS CONCERNS REGARDING CONTAINER CLOSURE AND OXYGEN HEADSPACE HOWEVER, ALL CHEMISTS ARE IN AGREEMENT THAT THE DISCOLORATION OF THE RING IS DUE TO OXIDATION. . DIVISION WILL PROPOSE TO DR. BOTSTEIN (OFFICE LEVEL) AN INTERIM SOLUTION TO GET THE DRUG ON THE MARKET WITH A LONG TERM SOLUTION AGREED UPON BY NYCOMED.

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		06-AUG-97	TEL	V-115	. CSO WOULD NOT SPECULATE ON OUTCOME OF MEETING WITH DR. BOTSTEIN, HOWEVER, THE CSO DID SAY THAT A NONAPPROVABLE LETTER IS ALSO A POSSIBILITY.
		19-AUG-97	TEL	V-115	THE LATEST UPDATE FOR THE REVIEW IS THE, MEETING WITH DR. BOTSTEIN WILL NOT BE SCHEDULED UNTIL THE REVIEWING CHEMIST RETURNS FROM VACTION THIS WEEK.
		27-AUG-97	TEL	V-115	THE CSO CONTACTED DRA TO INFORM THAT, THE INTERNAL FDA MEETING TO DISCUSS THE CMC ISSUES FOR TESLASCAN WITH DR. BOTSTEIN (DIRECTOR,ODE III) WILL BE HELD 03-SEP-97. THE CSO WILL CONTACT NYCOMED DURING THE WEEK OF 08-SEP-97 WITH AN UPDATE ON THE DISCUSSIONS OF THIS MEETING.
		16-SEP-97	TEL	V-115	FDA CALLED TO PROVIDE AN UPDATE, OF THE TESLASCAN REVIEW. THE CHEMISTS HAVE REACHED A CONSENSUS ON A PLAN OF ACTION. DR. LOVE MET WITH CR. BOTSTEIN BUT NO DECISON WAS REACHED. NYCOMED WOULD MOST LIKELY HEAR DIVISIONS DECISION THROUGH AN OFFICIAL ACTION LETTER BEFORE 02-DEC-97. WHILE NO DEFINITIVE INFORMATION COULD BE PROVIDED THE CSO WAS NOT ENCOURAGING ABOUT THE CHEMIST'S RECOMMENDATIONS.
		24-SEP-97	TEL	V-115	DRA NAD FDA DISCUSSED THE THE STATUS OF THE, ACTION PACKAGE. . AN APPROVABLE OR NON-APPROVALBE ACTION LETTER HAS BEEN AUTHORED BUT IS AWAITING DR. BOTSTEIN'S FINAL REVIEW, DECISION ON ACTION AND SIGNATURE. IT IS ANTICIPATED IT CAN BE ISSUED WITHIN THE NEXT TWO WEEKS. . THE FDA COMMETNS ARE AIMED AT "CONTAINER/CLOSURE SYSTEM AND STOPPERS."
		07-OCT-97	TEL	V-115	FDA IS PLANNING TO HAVE THE ACTION LETTER, FINALIZED AND AVAILABLE FOR US BY 17-OCT-97.
		27-OCT-97	TEL	V-115	FDA CALLED WITH AN UPDATE ON THE ACTION, PACKAGE. DR. BOTSTEIN (OFFICE LEVEL DIRECTOR) HAS REVIEWED THE ACTION PACKAGE AND DOES NOT AGREE WITH THE DIVISION'S RECOMMENDATION FOR NONAPPROVAL. A FINAL DECISION REGARDING

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		27-OCT-97	TEL	V-115	THE ACTION HAS NOT BEEN MADE.
		29-OCT-97	TEL	V-115	FDA NOTIFIED NYCOMED THE MEETING BETWEEN, THE OFFICE OF NEW DRUG CHEMISTRY (ONDC) AND DIVISION OF MEDICAL IMAGING IS SCHEDULED FOR 04-NOV-97. A MEETING BETWEEN ONDC, DIVISION OF MEDICAL IMAGING AND DR.BOTSTEIN IS TENTATIVELY SCHEDULED FOR 07-NOV-97.
		04-NOV-97	TEL	V-115	A TELECONFERENCE WAS HELD TO DISCUSS, ADDITIONAL ISSUES ON TESLASCAN. THE DIVISION IS REQUESTING A FULL COLOR "MOCK-UP" OF THE VIAL LABEL, PACKAGE AND SHIPPING CARTONS WHICH STATE THAT THE PRODUCT MUST BE STORED ON ITS SIDE. THESE ITEMS MUST BE PROVIDED BY MONDAY, 10-NOV-97, AND WILL PLAY A PIVOTAL ROLE IN THE FINAL ACTION REGARDING THIS PRODUCT.
		06-NOV-97	SUB	V-115	DRA SUBMITTED REQUESTED INFORMATION IN RESPONSE TO TELEPHONE CONTACT OF 04-NOVEMBER-97. SUBMITTED FOR REVIEW WERE FIVE COLOR COPIES OF THE TESLASCAN VIAL AND CARTON LABEL, AND A BLACK AND WHITE COPY OF THE TESLASCAN SHIPPER. ON THE CARTON LABEL, WE HAVE PLACE THE STATEMENTS: "STORE VIAL ON SIDE IN ORIGINAL CARTON. DO NOT STORE VIAL UPRIGHT. UPRIGHT STORAGE MAY CAUSE OXIDATION OR DISCOLOR-ATION." WE UNDERSTAND THAT THIS WAS NOT PART OF FDA'S REQUEST, HOWEVER WE ARE ADDING THE FOLLOWING STATEMENTS TO THE VIAL LABEL AS A REMINDER TO THE CUSTOMERS TO COMPLY WITH OUR STORAGE CONDITIONS, DO NOT STORE VIAL UPRIGHT. UPRIGHT STORAGE MAY CAUSE OXIDATION OR DISCOLORATION." THIS SUBMISSION WAS SENT IN DUPLICATE AND A FORM FDA 356H WAS ATTACHED.
		14-NOV-97	SUB	V-115	IN RESPONSE TO TELEPHONE CONTACT OF 14-NOV-97, DRA IS SUBMITTING THE FOLLOWING: THE LATEST COLOR COPY OF THE REVISED TESLASCAN CARTON LABEL. PLEASE NOTE THAT THE STATEMENTS NOW APPEAR PROMINENTLY ABOVE THE PRODUCT LOGO. WE ARE SUBMITTING FIVE COPIES OF EACH LABEL FOR REVIEW.

OIPE JC3 JAN 14 1998 PATENT & TRADEMARK OFFICE

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re U.S. Patent of:

Scott M. Rocklage, et al.

U.S. Serial No.: 07/047,614
Filed: May 8, 1987

U.S. Patent No.: 4,933,456
Issued: June 12, 1990

For: DIPYRIDOXYL PHOSPHATE NMRI CONTRAST AGENTS

Group Art Unit: 121

Examiner: Alan L. Rothman

DECLARATION

Hon. Commissioner of Patents and Trademarks
Washington, D.C.

Sir:

JOHN KAPPOS, as patent counsel for Nycomed Salutar, Inc. of 466 Devon Park Drive, Wayne, PA 19087-8630 (hereinafter "Applicant"), by change of name from Salutar, Inc., the assignee of record of the above-identified patent (hereinafter "The Patent"), declares as follows:

CERTIFICATE OF MAILING UNDER 37 CFR 1.10

I hereby certify that this document (along with any referred to as being attached or enclosed) is being deposited with the United States Postal Service on the date shown below with sufficient postage as Express Mail (Label No. EM424912382US) in an envelope addressed to the Hon. Commissioner of Patents and Trademarks, Washington, D.C., 20231.

Date: Jan 14, 1998 Sent by: Cynthia B. Pacheco Signature: Cynthia B Pacheco

(1) THAT he is a registered patent attorney and an associate with the firm of Lyon & Lyon LLP, 633 West Fifth Street, 47th Floor, Los Angeles, California 90071-2066, authorized to practice before the United States Patent and Trademark Office under Registration No. 37,861, and that he is authorized by Applicant to file the accompanying Application For Extension of Patent Term Under 35 U.S.C. § 156, and to execute this Declaration.

(2) THAT, upon information and belief, Applicant is the assignee of the entire rights, title and interest in and to The Patent by reason of an Assignment to Salutar, Inc.[1/] recorded in the Assignment Records of the United States Patent and Trademark Office on May 8, 1987 at Reel 4750, Frame 972.

(3) THAT submitted herewith is an Application for Extension of Patent Term Under 35 U.S.C. § 156 for The Patent (hereinafter referred to as the "Application") requesting a 1628 day extension of term of The Patent.

(4) THAT he has reviewed and understands the contents of the Application being submitted pursuant to 37 CFR § 1.740.

(5) THAT he believes The Patent is subject to extension pursuant to 37 CFR § 1.710.

[1/] By change of name, now Nycomed Salutar, Inc.

(6) THAT he believes an extension of 1628 days as requested in the Application is justified under 35 U.S.C. § 156 and the applicable regulations; and

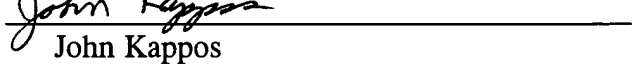
(7) THAT he believes The Patent meets the conditions for extension of the term of a patent as set forth in 37 CFR § 1.720.

He declares further that all statements made herein of his own knowledge are true and that all statements made on information and belief are believed to be true.

Respectfully submitted,

LYON & LYON LLP

Date: January 14, 1998

By 
John Kappos
Reg. No. 37,861
Attorneys for Applicants

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(714) 751-6606 or (213) 489-1600

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Scott M. Rocklage et al.

U.S. Serial No. 07/047,614
Filed: May 8, 1987

U.S. Patent No.: 4,933,456
Issued: June 12, 1990

For: DIPYRIDOXYL PHOSPHATE
NMRI CONTRAST AGENTS

Group Art Unit: 121

Examiner: A. Rothman

CERTIFICATE OF DUPLICATE

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

The undersigned hereby certifies that a duplicate of the original Application for Extension of Patent Term under 35 U.S.C. §156, including THE EXHIBITS and supporting papers, is being submitted herewith.

Respectfully submitted,

LYON & LYON LLP

Date: January 14, 1998

By John Kappos
John Kappos
Reg. No. 37,861
Attorneys for Applicants

JCK/cp
633 West Fifth Street, 47th Floor
Los Angeles, CA 90071-2066
(714) 751-6606 or (213) 489-1900

CERTIFICATE OF MAILING UNDER 37 C.F.R. 1.10

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Date: January 14, 1998 Sent by: Cynthia B. Pacheco Signature: Cynthia B Pacheco

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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Examiner: Alan L. Rothman

POWER OF ATTORNEY BY ASSIGNEE OF ENTIRE INTEREST

Hon. Commissioner of Patents and Trademarks
Washington, D.C. 20231

Sir:

I, Alan Watson, Senior Vice President of Nycomed Salutar, Inc., as representative of the Assignee of record of the entire interest of the above-identified patent, hereby appoint the following attorneys and/or agents to prosecute and transact all business in the Patent and Trademark Office connected specifically with, and limited to, the filing on its behalf of any application for extension of the patent term thereof under 35 U.S.C. § 156:

> The registered attorneys listed below and members of or associates in the law firm of **LYON & LYON**, 633 West Fifth Street, 47th Floor, Los Angeles,

CERTIFICATE OF MAILING UNDER 37 CFR 1.10

I hereby certify that this document (along with any referred to as being attached or enclosed) is being deposited with the United States Postal Service on the date shown below with sufficient postage as Express Mail (Label No. EM424912382US) in an envelope addressed to the Hon. Commissioner of Patents and Trademarks, Washington, D.C., 20231.

Date: Jan 14, 1998 Sent by: Cynthia B. Pacheco Signature: Cynthia B Pacheco